ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

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For surgical procedures
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Long-acting muscle relaxation without vagolytic effects

- Does not cause elevation of heart rate or blood pressure.[2]
- Recommended when cardiovascular stability is desired.[3]
- A useful alternative to pancuronium in patients where tachycardia is best avoided.[4]
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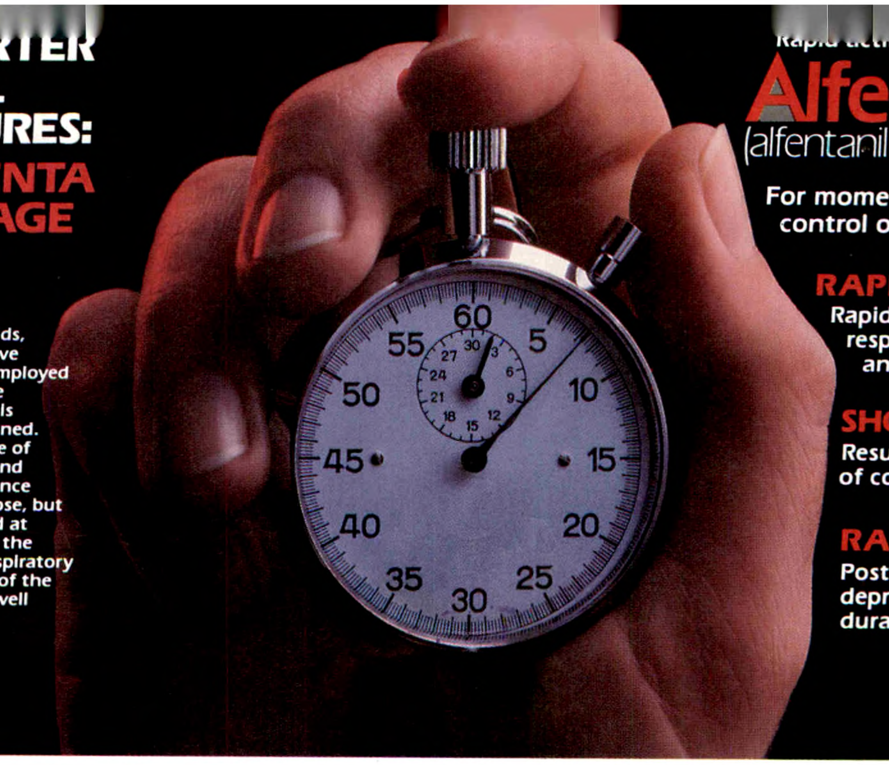

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Rapid-acting

Alfenta
(alfentanil HCl) Injection CII

For moment-to-moment control of stress responses

RAPID ONSET
Rapidly blocks sympathetic responses to induction and intubation

SHORT DURATION
Results in quick recovery of consciousness*

RAPID RECOVERY
Postoperative respiratory depression is of short duration*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

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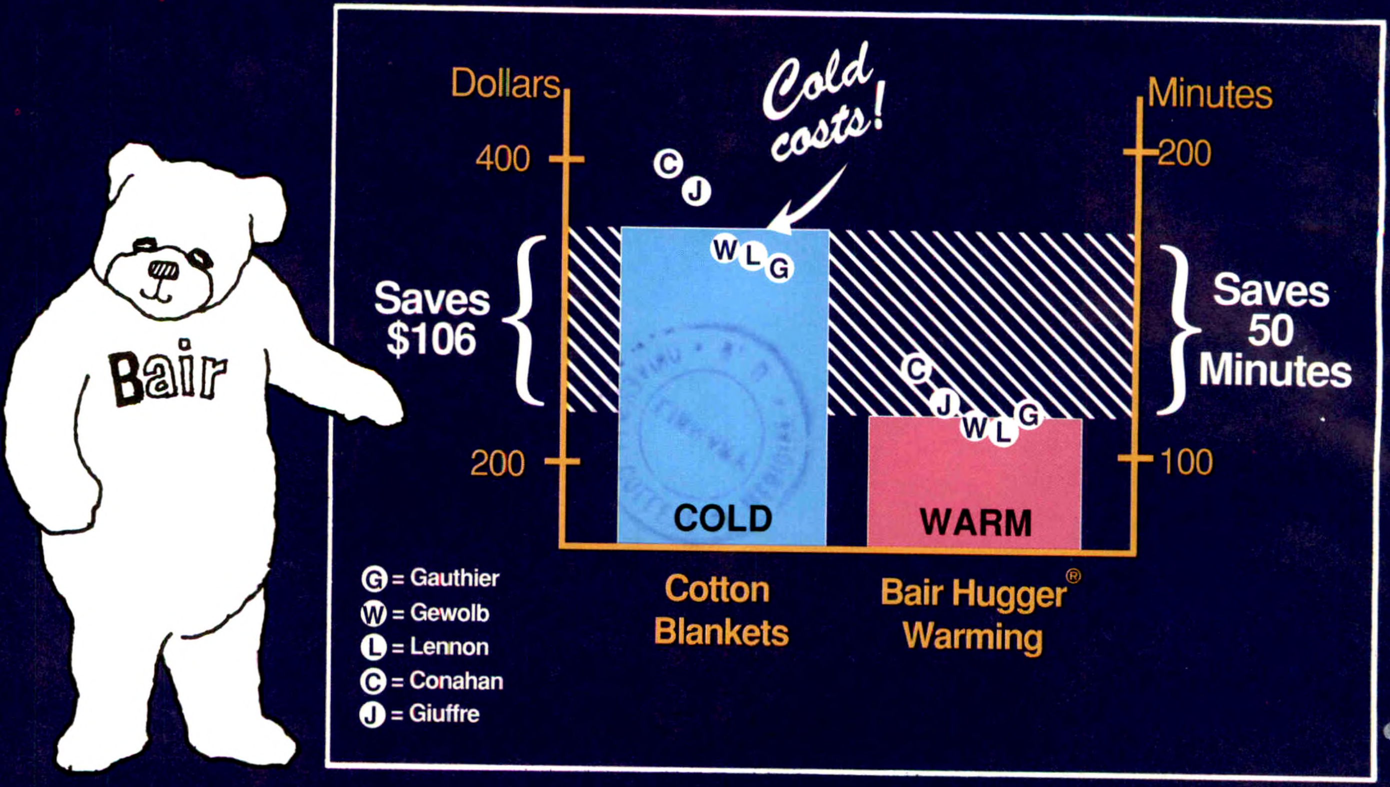

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Lennon RL, Hosking MP, Conover MA, Perkings WJ: Evaluation of a Forced-Air System for Warming Hypothermic Postoperative Patients. Anesthesia and Analgesia 70:424-427, 1990. Gauthier RL: Use of a Forced-Air Warming System for Intraoperative Warming. Anesthesiology 73:3A, 1990. Gewolb J, Hines R, Barash PG: A Survey of 3244 Admissions to the Post Anesthesia Recovery Room at a University Teaching Hospital. Anesthesiology 67:A471, 1987. Guiffre M, Finnie J, Lynam D, Smith D: Rewarming Postoperative Patients: Lights, Blankets or Forced Warm Air. (In Press, 1991). Conahan TJ, et al: Airway Heating Reduces Recovery Time (Cost) in Outpatients. Anesthesiology 67:128-130, 1982. Vosskuhler R: PACU Costs in the United States. Augustine Medical Press, 1990.

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EDITORIAL

Lectures in Anesthesia Training

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In this issue, Landers et al. (1) report the results of a survey on "lecture" practices in 100 university-affiliated residency programs. Most programs surveyed conducted at least one didactic session per week in the morning, but held most sessions sometime in the afternoon; some held sessions in the evening. The one statistically significant finding in the study was a direct correlation between programs' pass rates on the American Board of Anesthesiology (ABA) written examination and the percentage of residents attending morning sessions. However, the coefficient of determination, r^2, was 0.09, meaning, as the authors comment, that only 9% of the variability of the examination pass rates could be accounted for by the regression prediction. This study provides little insight into the role of lectures in residents' learning. The article is a good description of certain aspects of lecture practices but is not a prescription for what to do or how to do it better.

What other aspects of lectures might account for part of the other 91% of the variability in examination scores? The role of lectures in education has been a subject for research since 1925 when Bane (2) compared examination performance after lectures versus classroom discussions. He found no differences in immediate test scores but higher scores for the discussion method on delayed testing. Subsequently, there were conflicting reports: Costin (3) reviewed research on lecturing and found two reports showing superiority of lectures over discussions, five demonstrating that discussions produced more learning than lectures, and 13 revealing no significant difference. The results varied according to the specific outcomes that were measured. Solomon et al. (4) reported that lecture-oriented classes taught facts better but active-learning classes led to better comprehension. Bennett (5) contrasted formal (lecture-oriented) with informal (discussion-oriented) reading classes of 10–11-yr-old children. He found that formal classes improved reading scores more in boys who had higher initial reading scores. In contrast, informal classes created higher scores in boys who had lower initial scores. There was no significant difference between types of classes for girls. In a similar study of math classes, however, better outcomes for all students were obtained in formal rather than in informal classes (5). McKeachie (6) compared highly structured, teacher-centered classes emphasizing lecture and recitation with learner-centered classes that emphasized discussion. He found that structured classes led to higher scores on the final examination, but discussion classes produced better student performance on problems requiring analytical, synthetic, or evaluative skills. He commented that differences in students' anxiety about knowing what was expected of them contributed to the results. The message of all of this is that no generalizations about lectures versus discussion classes apply to all students or to all kinds of learning.

The effects of quality of lecture delivery on learning were investigated in a number of "Dr. Fox" papers. The first paper demonstrated that an actor with no knowledge of a subject could present an entertaining but almost meaningless lecture and satisfy the learners with the quality of the lecture (7). Subsequent studies (8–11) demonstrated that lecturers who show enthusiasm, humor, expressiveness, and charisma not only satisfy their students more but also stimulate higher students' scores on achievement tests.

Other aspects of lecturing have been studied. A paper by Brinkley, reviewed by Costin (3), reported that students in discussion classes had greater "mental alertness" than those in lectures. A study by Bloom (3) stated that "irrelevant thoughts" and "relevant thoughts of simple comprehension" occurred more often during lectures but thoughts concerning problem-solving and synthesis of material were more common during discussion classes. In a study by Stuart (12), medical students rated their concentration every 5 min during a 50-min lecture. Their concentration peaked at about 10–15 min and fell steadily for the remainder of the lecture. Lastly, the density of material delivered alters fact recall. Russell et al. (13), in their study of medical students' memory of basic, factual information, showed that both immediate and delayed recall of facts decreased as the

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number of new facts per lecture increased. The authors suggested that one-half of lecture time should be spent presenting new material; the other half should reinforce and explain that material.

These are a few of the educational effects of lectures that may account for some of the 91% unexplained variability in the findings reported by Landers et al. As the authors state, learning modalities other than lectures (individual study, reading, informal discussions, operating room experience, and one-to-one teaching) probably account for most of the variability.

Although their paper is titled, "Lecture Practices in United States Anesthesiology Residencies" and this discussion reviews studies on the educational value of lectures, it is likely that many of the "lectures" reported in the survey were other kinds of didactic sessions: case presentations, discussions, seminars, or journal clubs. Each of these educational formats has assets and liabilities different from those of lectures. George Miller, a father of research in medical education, wrote, "The question is not whether the lecture can be eliminated from the medical curriculum, but rather when can it be used to achieve a given set of objectives and how can it be used most effectively." It is appropriate for teachers to ask these questions of every teaching-learning session, both in the classroom and in the operating room.

References

1. Landers DF, Becker GL, Newland MC, Peters KR. Lecture practices in United States anesthesiology residencies. Anesth Analg 1992;74:112–5.
2. Bane CL. The lecture vs. the class discussion method of college teaching. School and Society 1925;21:300–2.
3. Costin F. Lecture versus other methods of teaching: a review of research. Br J Educ Technol 1972;3:4–31.
4. Solomon D, Rosenberg L, Bezdek WE. Teacher behavior and student learning. J Educ Psychol 1964;55:23–30.
5. Bennett N. Teaching styles and pupil progress. London: Open Books, 1976:79–97.
6. McKeachie WJ. Does anxiety disrupt information processing or does poor information processing lead to anxiety? Int Rev Appl Psychol 1984;33:187–203.
7. Naftulin DH, Ware JE Jr, Donnelly FA. The Doctor Fox lecture: a paradigm of educational seduction. J Med Educ 1973;48: 630–5.
8. Abrami PC, Leventhal L, Donnelly FA. Educational seduction. Rev Educ Res 1982;52:446–64.
9. Ware JE Jr, Williams RG. The Dr. Fox effect: a study of lecturer effectiveness and ratings of instruction. J Med Educ 1975;50: 149–56.
10. Williams RG, Ware JE Jr. An extended visit with Dr. Fox: Validity of student satisfaction with instruction ratings after repeated exposures to a lecturer. Am Educ Res J 1977;14:449–57.
11. Whitman N, Burgess PR. Teaching basic science: Dr. Fox in the physiology chicken coop. Med Educ 1988;22:393–7.
12. Stuart J. Medical student concentration during lectures. Lancet 1978;ii:514–6.
13. Russell IJ, Hendricson WD, Herbert RJ. Effects of lecture information density on medical student achievement. J Med Educ 1984;59:881–9.

CARDIOVASCULAR ANESTHESIA
Section Editor
Joseph G. Reves

A Randomized, Blinded, Placebo-Controlled Evaluation of Calcium Chloride and Epinephrine for Inotropic Support After Emergence From Cardiopulmonary Bypass

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Forty hemodynamically stable patients were randomized to receive an intravenous bolus of either calcium chloride (5 mg/kg) ($n = 20$) or placebo ($n = 20$) (phase I). Six minutes later, they received either an epinephrine (30 $ng\cdot kg^{-1}\cdot min^{-1}$) ($n = 20$) or placebo ($n = 20$) infusion (phase II). Hemodynamic and ionized calcium measurements were obtained in phase I at baseline and at 3 and 6 min after the bolus, and in phase II, at 3 and 6 min (study times 9 and 12 min) after initiation of the infusion. Compared with placebo, calcium did not significantly increase cardiac index but significantly increased mean arterial pressure. Calcium improved cardiac index from 2.46 ± 0.12 (mean ± SEM) to 2.74 ± 0.12 $L\cdot min^{-1}\cdot m^{-2}$; likewise, placebo improved cardiac index from 2.51 ± 0.15 to 2.74 ± 0.15 $L\cdot min^{-1}\cdot m^{-2}$. Mean arterial blood pressure increased with calcium from 74 ± 2 to 82 ± 3 mm Hg compared with a placebo change of 74 ± 2 to 76 ± 2 mm Hg. Patients who received the epinephrine infusion ($n = 20$) demonstrated a significant increase in cardiac index at time 12 min compared with patients receiving only placebo ($n = 20$). Cardiac index of the epinephrine group increased from 2.56 ± 0.15 to 2.92 ± 0.22 $L\cdot min^{-1}\cdot m^{-2}$, whereas in the placebo group it decreased from 2.86 ± 0.13 to 2.78 ± 0.12 $L\cdot min^{-1}\cdot m^{-2}$. Prior administration of calcium did not alter the subsequent response to epinephrine ($n = 10$) compared with patients receiving epinephrine alone ($n = 10$). We conclude that cardiac index improves with time without drug therapy after bypass. Calcium chloride increases mean arterial blood pressure but not cardiac index immediately after cardiopulmonary bypass, whereas low-dose epinephrine significantly increases both cardiac index and mean arterial blood pressure without causing tachycardia in these patients. Calcium chloride (5 mg/kg) did not augment or inhibit the hemodynamic response to an epinephrine infusion.

(Anesth Analg 1992;74:3–13)

Calcium is essential for myocardial contraction (1), and severe hypocalcemia may lead to myocardial depression and vasodilation (2). Hypocalcemia occurs commonly during cardiopulmonary bypass because of hemodilution from the crystalloid pump prime (3), calcium binding by citrate from blood products (4), calcium binding induced by heparin administration (5), and calcium binding by albumin given to increase plasma colloid osmotic pressure (6). However, in a recent study of coronary surgery patients, blood-ionized calcium levels decreased during cardiopulmonary bypass, but approached normal values immediately before separation from bypass (7). Despite the return to eucalcemia (which may go unrecognized unless ionized calcium measurements are performed before separation from bypass), calcium is still frequently administered during emergence from cardiopulmonary bypass for its vasopressor and supposed inotropic effects (8,9).

The American Heart Association no longer recommends routine calcium administration during cardiopulmonary resuscitation (10–15). Moreover, mounting experimental data link increased intracellular calcium levels with cell injury and cell death during ischemia and reperfusion (16), a sequence that occurs routinely during coronary surgery as a consequence of aortic clamping. Additionally, calcium administration may reduce the inotropic potency of a subse-

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quent epinephrine or dobutamine infusion (17,18), which is often required when ventricular function deteriorates during the immediate postpump reperfusion period. For these reasons, if calcium lacks clinical efficacy after cardiopulmonary bypass, then its use in this setting might be inappropriate.

We designed a randomized, blinded, placebo-controlled study to answer the following questions: (a) Does intravenous calcium chloride (compared with a placebo control group) increase cardiac index and mean arterial pressure? (b) Is calcium as effective as epinephrine at increasing cardiac index? (c) Does calcium add to or inhibit the hemodynamic effects of epinephrine? Despite the frequent use of calcium and epinephrine after cardiopulmonary bypass, no placebo-controlled trial of either calcium or epinephrine has been performed in this setting.

Methods

The study was approved by the institutional review board for clinical research and consisted of 40 patients with normal preoperative left ventricular function undergoing coronary artery bypass grafting. Written, informed consent was obtained from patients preoperatively. Exclusion criteria included use of long-acting β-blocking agents (e.g., atenolol and nadolol), disorders of calcium metabolism, valvular or congenital heart disease, and ejection fractions less than 0.45 measured during left ventriculography by cardiologists. All patients received high doses of narcotics (fentanyl 50–100 μg/kg or sufentanil 10–30 μg/kg), muscle relaxants (pancuronium 0.1–0.2 mg/kg or metocurine 0.2–0.6 mg/kg), and amnestics (midazolam 0.1–0.3 mg/kg or lorazepam 0.03 mg/kg) for the anesthetic regimen. All operations were performed during cold potassium blood cardioplegia with moderate total body hypothermia (28°C). Patients were studied immediately after full rewarming (36–37°C rectally) and discontinuation of cardiopulmonary bypass. Seven additional consenting patients required immediate inotropic therapy and were excluded from the study. If a phenylephrine infusion (10–100 μg/min) was required to maintain adequate perfusion pressure (>50 mm Hg) during rewarming and to stabilize systolic arterial pressure (≥90 mm Hg) after separation from bypass (before initiation of the study), we continued phenylephrine infusion at the same rate throughout the study period.

To compare the effects of calcium versus a control, patients were randomized in phase I to receive either a calcium bolus (5 mg/kg) or a placebo bolus. Six minutes later, patients were again randomized to receive either epinephrine (30 $ng \cdot kg^{-1} \cdot min^{-1}$) or placebo infusion to compare the effects of epinephrine, calcium, and placebo, and any interaction between calcium and epinephrine (phase II). Data were collected for an additional 6 min during phase II. After removal of the venous cannulas, all surgery was discontinued during the study period. The study period was limited to 12 min to allow continuation of surgery, subsequent protamine administration, and removal of the aortic cannulas. The investigator administering the drugs and collecting data was blinded to the identity of the bolus and infusion. All study drugs administered were prepared by a research nurse (L.M.D.). Our study design in phase I resulted in two patient groups for comparison, (a) calcium (n = 20) and (b) placebo (n = 20). Our combined drug assignments in phase II resulted in four patient groups for comparison: (a) placebo bolus+placebo infusion (n = 10), (b) placebo bolus+epinephrine infusion (n = 10), (c) calcium bolus+placebo infusion (n = 10), and (d) calcium bolus+epinephrine infusion (n = 10).

Blood ionized calcium levels were measured in anaerobically collected blood samples using the Nova II ion-selective electrode (Nova Biomedical, Waltham, Mass.). The instrument was standardized with known low, normal, and high ionized calcium levels with imprecision expressed as the coefficient of variation <1.0%. Calibration is completely automated with two internal standards. Normal levels in our laboratory are 1.05–1.25 mM. Thermodilution cardiac outputs were measured in duplicate at end-expiration of the respiratory cycle. Systolic, diastolic, and mean arterial blood pressures; systolic, diastolic, and mean pulmonary artery pressures; and central venous pressure were measured using the radial artery cannula and pulmonary artery catheter inserted preoperatively. We maintained pulmonary artery diastolic pressure at a constant value (12–15 mm Hg) during the study by transfusion of blood from the pump-oxygenator reservoir. Heart rate was maintained constant (90 beats/min) by atrial or atrioventricular pacing. Electrocardiographic leads II and V_5 were monitored continuously for return to sinus rhythm during the study. In phase I, immediately after baseline data collection (time 0), the patients received either a blinded intravenous bolus of calcium chloride (5 mg/kg) or an identical volume of placebo (normal saline). Data collection was repeated 3 and 6 min after the bolus injection. Next, in phase II, a randomly assigned, blinded infusion of either epinephrine (30 $ng \cdot kg^{-1} \cdot min^{-1}$) or placebo (normal saline) was started. Data collection was repeated at study times 9 and 12 min (3 and 6 min after the initiation of the infusion). The study was completed after the 12-min measurement. We therefore collected data at five time points during the 12-min study: 0, 3, 6, 9, and 12 min.

Table 1. Patient Demographic Data

	Placebo-placebo (n = 10)	Placebo-epinephrine (n = 10)	Calcium-placebo (n = 10)	Calcium-epinephrine (n = 10)	Significance[a] ($P < 0.05$)
Age (yr)[b]	59 ± 3	62 ± 4	59 ± 3	59 ± 3	NS
Sex (M:F)	10:0	8:2	10:0	9:1	NS
Weight (kg)[b]	82 ± 4	83 ± 4	86 ± 3	86 ± 7	NS
Left ventricular ejection fraction (%)[b]	62 ± 4	54 ± 4	59 ± 3	61 ± 3	NS
Antianginal drugs[c]					
β-Blockers (n)	2	2	6	5	$P = 0.051$[d]
Calcium channel blockers (n)	7	7	3	8	NS
Long-acting nitrates (n)	9	9	8	7	NS
Reinfused volume[b] (mL)	350 ± 50	400 ± 100	300 ± 100	250 ± 100	NS
Phenylephrine (10–100 μg/min) (n)[c]	9	5	4	5	NS
Cross-clamp time (min)[b]	63 ± 10	55 ± 4.0	50 ± 7.9	51 ± 6.5	NS
Bypass time (min)[b]	123 ± 12	107 ± 12	104 ± 16	119 ± 15	NS

NS, not significant.
[a] Statistical comparisons with χ^2 analysis with and without Yates' correction comparing placebo (n = 20) versus calcium (n = 20) and all four groups.
[b] Values are expressed as mean ± SEM.
[c] Number of patients out of each group receiving the drug indicated.
[d] Comparing patients receiving placebo (n = 20) versus those receiving calcium (n = 20).

Statistical comparisons within a study group were determined by repeated measures analysis of variance and Dunnett's multiple range test. Between-group comparisons were analyzed by one-factor analysis of variance at each time point. Calcium or epinephrine effect was examined by two-factor repeated measures analysis of covariance. Correlations between baseline and post-calcium ionized calcium values and cardiac index and mean arterial pressure were tested by linear regression analysis. Demographic data were compared by χ^2 analysis with and without Yates' correction. $P < 0.05$ was considered significant for all statistical tests. All statistical analyses were carried out using STATVIEW 512+ software (Brainpower, Inc., Calabasas, Calif.) and True Epistat (Epistat Services, Richardson, Tex.)

Results

Demographics

Demographic data for the four patient groups are given in Table 1. There were no differences in preoperative ejection fraction, age, weight, or gender among the groups. There were no statistically significant differences between groups with regard to preoperative medications or the use of phenylephrine. The patients receiving calcium (n = 20) were more likely to be receiving β-blockers (11 of 20) preoperatively than the placebo group (4 of 20) ($P = 0.051$). The importance of β-blockers in influencing the response to calcium is considered in the next section. The volume of blood transfused from the pump reservoir to maintain pulmonary artery diastolic pressure during the study, the duration of cardiopulmonary bypass, and the duration of aortic cross-clamping did not differ among the four groups. Complete hemodynamic data for phase I and phase II of the study are given in Tables 2–4.

Intravenous Calcium Versus Placebo (Phase I)

The patients receiving 5 mg/kg calcium chloride intravenously (n = 20) demonstrated significant increases in blood ionized calcium concentration from 0.99 ± 0.02 mM to 1.21 ± 0.04 mM ($P < 0.05$; Figure 1). Ionized calcium concentrations remained significantly elevated in these patients throughout the study period (phases I and II). Blood ionized calcium concentration did not change in patients receiving placebo (n = 20) (Figure 1).

Calcium chloride administration significantly increased mean arterial blood pressure from 74 ± 2 mm Hg at time 0 to 82 ± 3 mm Hg at time 6 min ($P < 0.05$), significantly higher than the placebo group ($P < 0.05$) (Figure 2, Table 2). Mean arterial blood pressure remained constant throughout the first phase of the study in the placebo group. There was no correlation between mean arterial pressure and ionized calcium levels at time 0 for all patients (n = 40) (r = 0.14, P = 0.38) nor was there a correlation between the change in mean arterial blood pressure and the change in ionized calcium levels in the calcium group (n = 20) (r = 0.29, P = 0.21) comparing time 0 (baseline) with time 6 min.

Despite significant differences in ionized calcium levels, there was no difference in cardiac index between the calcium group and the placebo group at any of times 0, 3, and 6 min (Figure 3, Table 2). There

Table 2. Hemodynamic Data: Calcium Versus Placebo (Phase I)

	MAP (mm Hg)	CI ($L \cdot min^{-1} \cdot m^{-2}$)	SV (mL/beat)	PADP (mm Hg)	MPAP (mm Hg)	CVP (mm Hg)	SVR ($dyne \cdot s \cdot cm^{-5}$)	PVR ($dyne \cdot s \cdot cm^{-5}$)
Placebo ($n = 20$)								
0 min	74 ± 2.2	2.51 ± 0.15	56 ± 3.7	14 ± 1.2	22 ± 1.0	10 ± 0.7	1017 ± 63	136 ± 12
3 min	72 ± 2.0	2.67 ± 0.19^a	60 ± 3.9^a	12 ± 1.2	21 ± 0.9	10 ± 0.8	961 ± 66	122 ± 12
6 min	76 ± 2.1	2.74 ± 0.15^a	61 ± 3.8^a	13 ± 1.3	21 ± 0.9	10 ± 0.7	999 ± 69	119 ± 12
Calcium ($n = 20$)								
0 min	74 ± 2.4	2.46 ± 0.12	55 ± 2.8	13 ± 1.1	19 ± 0.7	11 ± 1.1	980 ± 70	112 ± 11
3 min	83 ± 2.9^{a,b}	2.64 ± 0.18^a	60 ± 2.9^a	14 ± 1.1	20 ± 0.8	10 ± 0.9	1049 ± 58	110 ± 16
6 min	82 ± 2.8^a	2.74 ± 0.12^a	62 ± 3.2^a	14 ± 1.0	20 ± 0.8	10 ± 0.9	1001 ± 71	96 ± 12

MAP, mean arterial blood pressure; CI, cardiac index; SV, stroke volume; PADP, pulmonary artery diastolic pressure; MPAP, mean pulmonary artery pressure; CVP, central venous pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance. (Heart rate was maintained constant at 90 beats/min and is not included.)

$^aP < 0.05$ compared with time 0.

$^bP < 0.05$ compared with placebo group.

Table 3. Hemodynamic Data: Epinephrine Versus Placebo (Phase II)

	MAP (mm Hg)	CI ($L \cdot min^{-1} \cdot m^{-2}$)	SV (mL/beat)	PADP (mm Hg)	MPAP (mm Hg)	CVP (mm Hg)	SVR ($dyne \cdot s \cdot cm^{-5}$)	PVR ($dyne \cdot s \cdot cm^{-5}$)
Placebo ($n = 20$)								
6 min	78 ± 2.6	2.86 ± 0.13	65 ± 3.6	14 ± 1.3	20 ± 0.9	11 ± 0.8	864 ± 71	93 ± 10.0
9 min	77 ± 2.5	2.83 ± 0.14	65 ± 3.9	13 ± 1.5	20 ± 0.9	10 ± 0.8	959 ± 54	95 ± 9.6
12 min	82 ± 2.7	2.78 ± 0.12	64 ± 3.6	13 ± 1.3	20 ± 0.9	10 ± 0.9	1000 ± 55	93 ± 8.5
Epinephrine ($n = 20$)								
6 min	80 ± 3.0	2.56 ± 0.15	58 ± 3.2	14 ± 1.0	22 ± 1.1	9 ± 0.8	1106 ± 69	122 ± 13
9 min	86 ± 3.4^a	2.81 ± 0.22^a	64 ± 4.5^a	15 ± 0.8	23 ± 1.0	9 ± 0.8	1136 ± 88	128 ± 16
12 min	88 ± 4.0^a	2.92 ± 0.22^a	66 ± 4.4^a	15 ± 1.0	24 ± 1.0	9 ± 0.8	1124 ± 96	134 ± 18

MAP, mean arterial blood pressure; CI, cardiac index; SV, stroke volume; PADP, pulmonary artery diastolic pressure; MPAP, mean pulmonary artery pressure; CVP, central venous pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

$^aP < 0.05$ compared with time 6 min.

was a significant, time-related increase in cardiac index in both groups compared with baseline (time 0) ($P < 0.05$). There was no correlation between cardiac index and ionized calcium levels at time 0 ($n = 40$) (Figure 4, $r = 0.04$, $P = 0.80$). Also, the change in ionized calcium in patients receiving calcium ($n = 20$) at time 6 min did not predict the change in cardiac index at time 6 min (Figure 4, $r = 0.17$, $P = 0.47$). Finally, neither calcium nor placebo significantly altered heart rate, systemic vascular resistance, pulmonary vascular resistance, central venous pressure, pulmonary artery pressure, or pulmonary artery diastolic pressure.

As a greater number of patients in the calcium group received preoperative β-blockers (11 of 20) than in the control group (4 of 20), we compared the hemodynamic effects of calcium in patients receiving preoperative β-blockers ($n = 11$) versus those not receiving preoperative β-blockers ($n = 9$). Comparing these patients, there was no significant difference at any time (0, 3, 6 min) in cardiac index or mean arterial blood pressure. The increase in cardiac index in the patients receiving β-blockers (0.25 ± 0.2 $L \cdot min^{-1} \cdot m^{-2}$) and in those not receiving β-blockers (0.30 ± 0.2 $L \cdot min^{-1} \cdot m^{-2}$) was not significantly different.

Finally, we tested whether administration of phenylephrine influenced the subsequent response to calcium. There was no significant difference between patients receiving ($n = 10$) or not receiving ($n = 10$) phenylephrine in the effect of calcium on cardiac index and mean arterial blood pressure.

Epinephrine Infusion Versus Placebo Infusion (Phase II)

As there were no significant differences in the cardiac output response of patients who received either calcium or placebo, we pooled data from all patients ($n = 40$) regardless of the bolus dose given (calcium or placebo) and compared patients receiving the epinephrine infusion ($n = 20$) with those receiving the placebo infusion ($n = 20$) (Figure 5, Table 3) comparing time 6 min to time 12 min. Cardiac index in the epinephrine patients increased significantly from 2.56 ± 0.15 to 2.92 ± 0.22 $L \cdot min^{-1} \cdot m^{-2}$ ($P < 0.05$). Cardiac index in the placebo patients decreased from 2.86 ±

Table 4. Hemodynamic Data Comparing Epinephrine Versus Calcium-Epinephrine

	MAP (mm Hg)	CI ($L \cdot min^{-1} \cdot m^{-2}$)	SV (mL/beat)	PADP (mm Hg)	MPAP (mm Hg)	CVP (mm Hg)	SVR ($dyne \cdot s \cdot cm^{-5}$)	PVR ($dyne \cdot s \cdot cm^{-5}$)
Placebo-epinephrine ($n = 10$)								
0 min	76 ± 3.2	2.37 ± 0.24	54 ± 4.3	15.2 ± 1.0	23.2 ± 1.3	9.9 ± 1.1	1083 ± 79	141 ± 16
3 min	75 ± 2.8	2.67 ± 0.32	60 ± 5.2	13.3 ± 0.8	21.2 ± 1.1	9.6 ± 1.2	1018 ± 99	190 ± 71
6 min	78 ± 3.6	2.65 ± 0.25	58 ± 5.0	14.2 ± 0.9	22.5 ± 1.2	9.3 ± 0.8	1090 ± 106	193 ± 67
9 min	84 ± 5.0^a	2.91 ± 0.38^a	65 ± 7.9^a	15.4 ± 0.8	25.1 ± 1.6	9.6 ± 1.0	1109 ± 131	200 ± 53
12 min	87 ± 6.0^a	2.94 ± 0.33^a	65 ± 6.7^a	15.7 ± 1.0	25.9 ± 1.5^a	9.5 ± 1.1	1131 ± 144	207 ± 46
Calcium-epinephrine ($n = 10$)								
0 min	74 ± 3.8	2.35 ± 0.20	51 ± 4.0	14.4 ± 1.2	22.2 ± 1.4	10.0 ± 1.8	1082 ± 81	128 ± 19
3 min	84 ± 3.8^a	2.50 ± 0.19	55 ± 4.0	14.4 ± 1.2	22.7 ± 1.9	9.9 ± 1.4	1139 ± 93	138 ± 28
6 min	82 ± 3.9	2.56 ± 0.18	57 ± 4.4	14.0 ± 1.0	21.5 ± 2.0	9.2 ± 1.2	1122 ± 95	113 ± 20
9 min	88 ± 3.9	2.75 ± 0.22^a	62 ± 4.9^a	14.8 ± 0.8	21.9 ± 1.6	8.5 ± 1.2	1262 ± 124	105 ± 22
12 min	89 ± 4.9^a	2.98 ± 0.29^a	67 ± 6.1^a	15.0 ± 1.0	22.7 ± 1.3	8.6 ± 1.2	1116 ± 135	106 ± 16

MAP, mean arterial blood pressure; CI, cardiac index; SV, stroke volume; PADP, pulmonary artery diastolic pressure; MPAP, mean pulmonary artery pressure; CVP, central venous pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

[a] $P < 0.05$ compared with time 0.

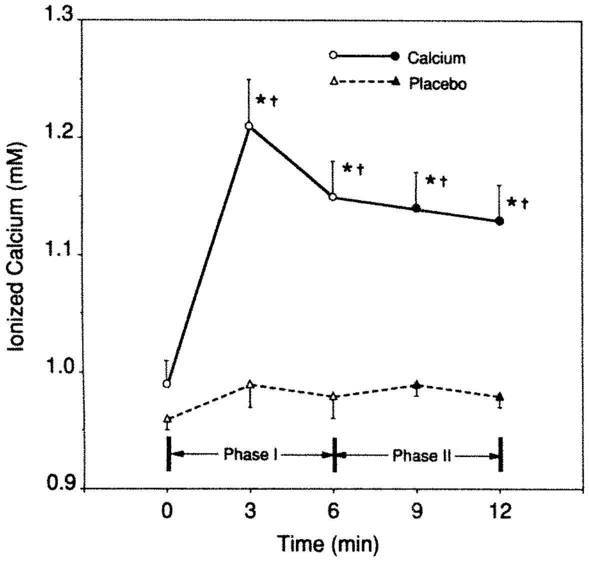

Figure 1. Ionized calcium levels in patients receiving intravenous calcium chloride (5 mg/kg) (*circles*) and placebo (*triangles*) over the entire study period. The data are expressed as mean values ± SEM. The *asterisk* denotes that the ionized calcium level is significantly increased ($P < 0.05$) compared to time 0. The *dagger* signifies that ionized calcium remains significantly higher at each point of the study period in the calcium group ($n = 20$) compared with the placebo group ($n = 20$). The *open symbols* denote phase I and the closed symbols phase II.

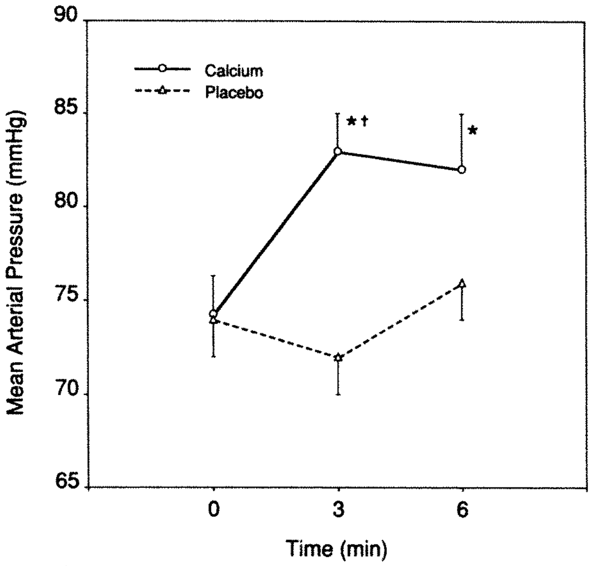

Figure 2. Mean arterial blood pressure comparing calcium ($n = 20$) (*circles*) and placebo ($n = 20$) (*triangles*) during phase I. At time 3 min, the *asterisk* denotes a significant increase in mean arterial blood pressure ($P < 0.05$) in patients receiving calcium compared to time 0. The *dagger* denotes a significant difference between the calcium and placebo groups at time 3 min ($P < 0.05$).

0.13 to 2.78 ± 0.12 $L \cdot min^{-1} \cdot m^{-2}$. Mean arterial blood pressure in the epinephrine group increased significantly from 80 ± 3 mm Hg at time 6 min to 88 ± 4 mm Hg at time 12 min ($P < 0.05$); there was no significant change in mean arterial blood pressure in the placebo group. There was no significant effect of epinephrine on heart rate (patients remained paced at 90 beats/min without sinus node competition), systemic vascular resistance, pulmonary vascular resistance, central venous pressure, pulmonary artery pressure, or pulmonary artery diastolic pressure.

Effect of Calcium on Response to Epinephrine Infusion (Phases I and II)

Patients who received epinephrine ($n = 20$) had previously received either calcium ($n = 10$) or placebo ($n = 10$). There were no significant differences between

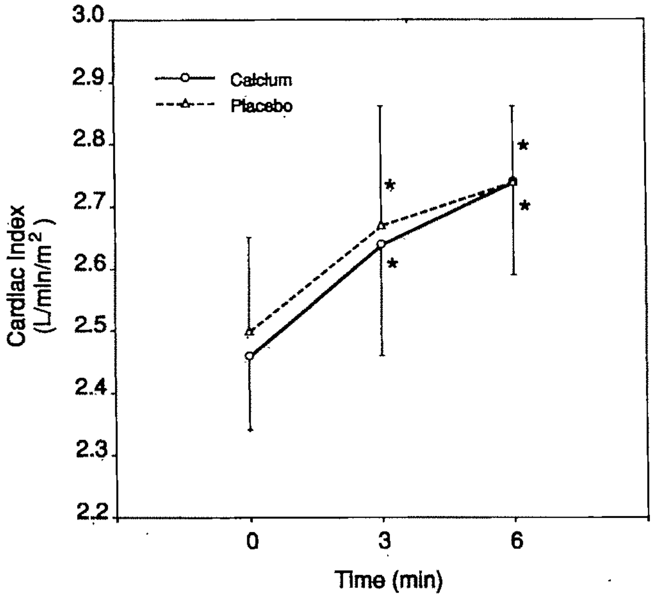

Figure 3. Cardiac index during the first phase of the study comparing calcium ($n = 20$) (*circles*) and placebo ($n = 20$) (*triangles*) groups. The *asterisk* denotes a significant increase in cardiac index in both groups compared to time 0 ($P < 0.05$). However, there was no difference between groups, indicating that an improvement in cardiac function occurs during the first few minutes after discontinuation of cardiopulmonary bypass despite calcium administration.

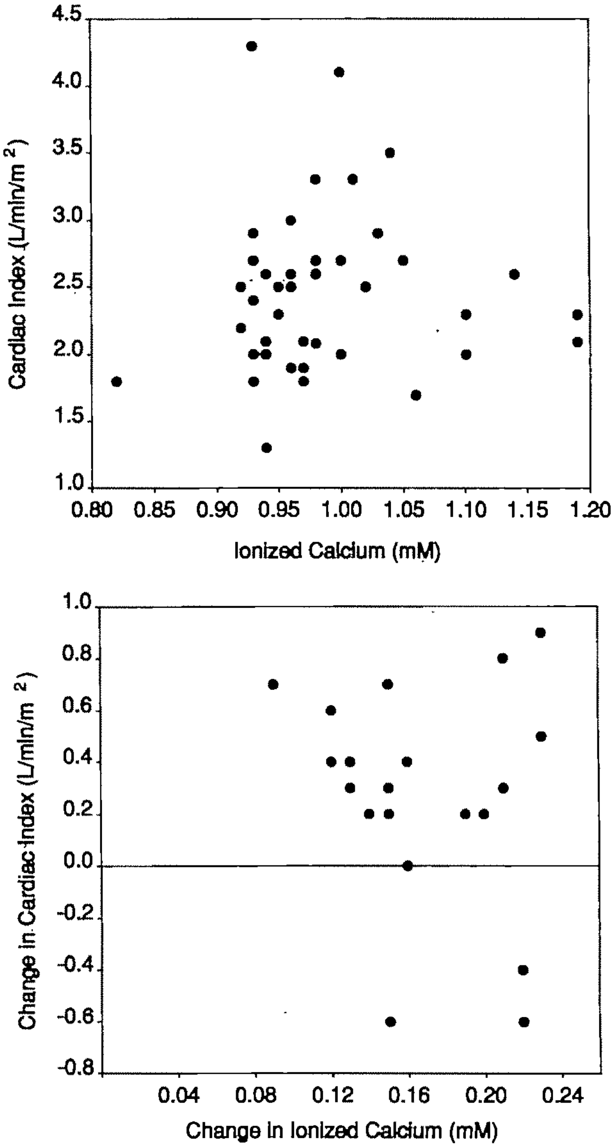

Figure 4. Scattergrams comparing cardiac index versus ionized calcium levels at time 0 ($n = 40$, *top panel*) and comparing the change in cardiac index versus the change in ionized calcium in patients receiving calcium at time 6 min ($n = 20$, *lower panel*). There was no correlation between cardiac index and ionized calcium in this patient population at low-normal, normal, and high-normal ionized calcium levels ($r = 0.04$, $P = 0.80$) and no correlation in the change in ionized calcium after calcium administration in predicting the resulting change in cardiac index at time 6 min ($r = 0.17$, $P = 0.47$).

the placebo-epinephrine patients and the calcium-epinephrine patients with regard to mean arterial blood pressure or cardiac index (Figure 6, Table 4). The increase in mean arterial blood pressure in the placebo-epinephrine and calcium-epinephrine groups at time 12 min was 14 ± 8 versus 15 ± 6 mm Hg, respectively. Similarly, cardiac index increased with placebo-epinephrine by 0.57 ± 0.17 $L \cdot min^{-1} \cdot m^{-2}$ compared with 0.63 ± 0.24 $L \cdot min^{-1} \cdot m^{-2}$ with calcium-epinephrine.

Discussion

Our study demonstrates that intravenous calcium chloride (5 mg/kg), despite providing a sustained increase in blood ionized calcium levels, is no more effective than placebo at increasing cardiac index in hemodynamically stable patients immediately after cardiopulmonary bypass. Calcium chloride (5 mg/kg) does produce a sustained increase in mean arterial blood pressure. However, there was no correlation between blood ionized calcium concentration and cardiac index (Figure 4) or mean arterial blood pressure either before or after calcium or placebo administration over a wide, clinically relevant range of ionized calcium levels. In contrast, Desai et al. (19) found a direct relationship between baseline blood ionized calcium levels and mean arterial blood pressure in patients with critical medical illness ($r = 0.43$, $P < 0.01$). Several studies have reported a linear relationship between ionized calcium levels and changes in myocardial contractility (20,21). Bristow et al. (20) studied open-chest dogs in which the heart was isolated from the effects of afterload; Lang et al. (21) studied only patients with uremia under differing afterload conditions with two-dimensional echocar-

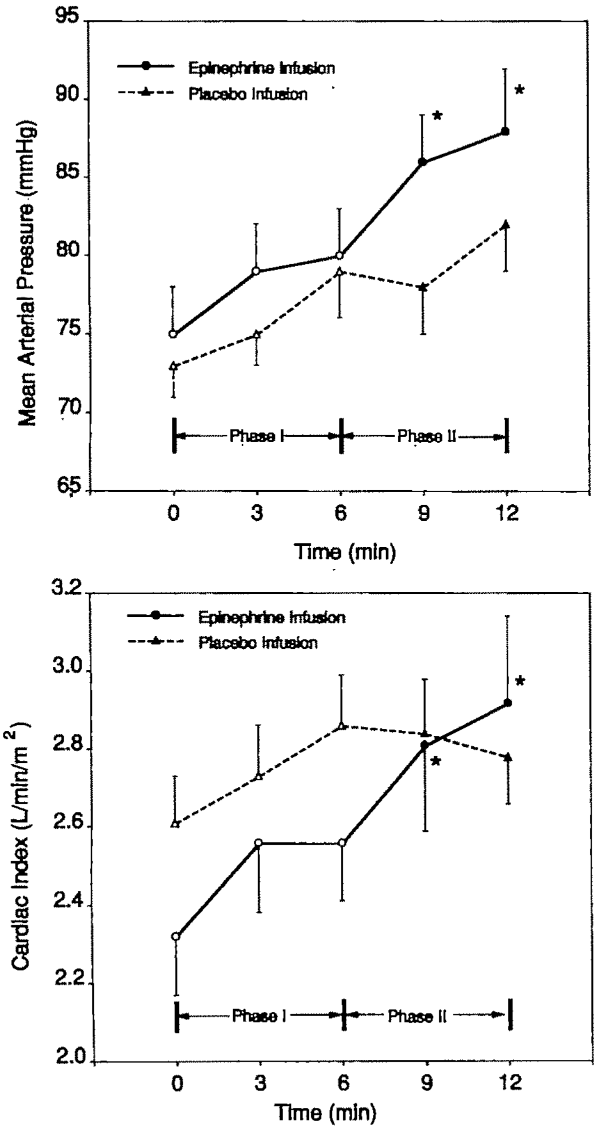

Figure 5. Mean arterial blood pressure (*top panel*) and cardiac index (*lower panel*) comparing epinephrine infusion ($n = 20$) (*closed circles*) and placebo infusion ($n = 20$) (*closed triangles*). In patients subsequently receiving epinephrine or placebo infusions during phase II, there was no statistical difference in mean arterial blood pressure or cardiac index between the groups during the first phase of the study (*open circles and triangles*). After the infusions (*closed circles and triangles*), the *asterisk* signifies that epinephrine significantly increased cardiac index and mean arterial blood pressure ($P < 0.05$) comparing time 6 min and time 12 min (phase II). Placebo infusion resulted in no change in either cardiac index or mean arterial blood pressure during phase II.

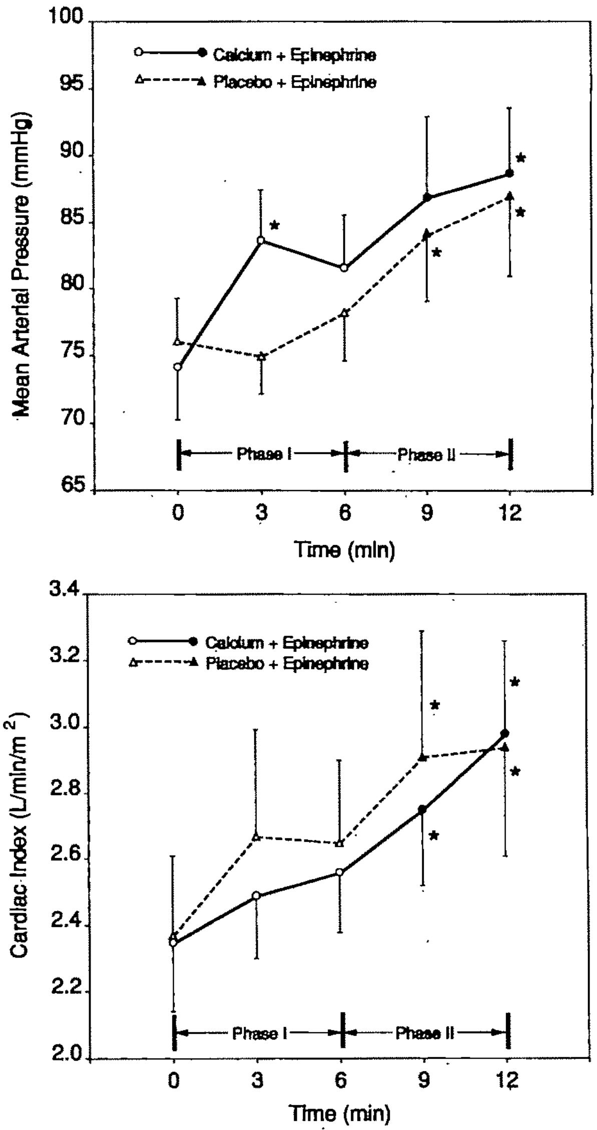

Figure 6. Mean arterial blood pressure (*top panel*) and cardiac index (*lower panel*) comparing the calcium+epinephrine ($n = 10$) (*circles*) and the placebo+epinephrine ($n = 10$) (*triangles*) groups over the entire study period. The *asterisk* signifies that mean arterial blood pressure and cardiac index were significantly higher ($P < 0.05$) compared to time 0. Cardiac index and mean arterial blood pressure were similar in both groups, showing no augmentation or inhibition by calcium (5 mg/kg) of epinephrine's hemodynamic effects.

diography. However, the increases in contractility reported in these two studies do not necessarily imply that cardiac output increased because of the important role of the systemic vasculature in regulating the hemodynamic responses to calcium (22). The failure of calcium to increase cardiac index in our study despite an increase in ionized calcium levels underscores this important interaction between simultaneous increases in contractility and afterload.

Previous Human Surgical Studies of Calcium

Numerous animal (4,23–25) and human studies (8,26–28) have evaluated the effects of calcium on myocardial contractility, cardiac output, and the peripheral vasculature, but few studies have considered the hemodynamic effects of calcium on patients immediately after discontinuation of cardiopulmonary bypass. Lappas et al. (29) found that 5 mg/kg of calcium chloride increased myocardial contractility, mean arterial blood pressure, and systemic vascular resistance, but did not significantly change cardiac index in 18 patients after coronary artery bypass grafting. In a combined study of dopamine and dobutamine, d'Hollander et al. (30) infused calcium chloride (0.6 g/m^2) over 30 s and measured hemodynamics 2 min later in 34 patients undergoing aortic valve replacement. They found that cardiac index, mean arterial blood pressure, and contractility, as measured by a left ventricular pressure transducer, all increased significantly at 2 min. Unfortunately, no patient received placebo, leaving a possible time-related (and calcium-unrelated) increase in cardiac index and blood pressure as an explanation for the observed effect. Shapira and colleagues (8) performed another study of calcium chloride immediately after cardiopulmonary bypass in 26 patients using pressure transducers in the left ventricle and electromagnetic flowmeters around the ascending aorta. After a bolus injection of 10 mg/kg of calcium chloride, cardiac index, contractility, and systemic blood pressure quickly increased. However, only contractility and systemic blood pressure (including systemic vascular resistance) remained elevated over the next 5 min. Curiously, cardiac index was elevated for less than 30 s despite continued elevation of the ionized calcium level. Thus, despite its continuing popularity in cardiovascular surgery, no study has demonstrated that calcium chloride is superior to placebo in increasing cardiac output and peripheral oxygen delivery after cardiopulmonary bypass.

Detrimental Effects of Calcium Administration

Despite improvements in myocardial protection with cardioplegic solutions during ischemic, hypothermic cardiopulmonary bypass, significant myocardial metabolic alterations continue to occur (31). Ischemia produces decreased aerobic and increased anaerobic metabolism, resulting in decreased oxygen utilization, decreased production of high-energy phosphates, and intracellular acidosis. Decreased levels of high-energy phosphates lead to an elevation of intracellular calcium as a consequence of the cell's failure to pump calcium back into the sarcoplasmic reticulum and out of the cell during diastole (32). Sustained increases in cytosolic calcium concentration lead to pathological increases in mitochondrial calcium concentration, uncoupling of mitochondrial energy production, activation of destructive cellular enzymes, and ultimately to worsening of ischemic injury (33). Increased diastolic intracellular calcium concentration in the vicinity of the contractile proteins leads to reduced diastolic compliance and impaired relaxation, whereas the decline in calcium storage in the sarcoplasmic reticulum results in systolic dysfunction and compromised myocardial contractility (34). During reperfusion after hypoxic injury, superoxide radicals are released from the mitochondria, which cause lipid peroxidation, destroying the integrity of the cell membrane, thus allowing further calcium entry into the cell. This results in ventricular dysfunction, popularly referred to as the "stunned myocardium" (35,36). Therefore, calcium administration immediately after cardiopulmonary bypass may be deleterious; however, the exact relationship between intravenous administration of calcium and levels of intracellular calcium remains unknown.

Other detrimental effects of calcium during emergence from cardiopulmonary bypass may relate to myocardial oxygen supply and demand. Calcium may reduce oxygen supply to the heart by constricting coronary arterial smooth muscle (9). Coronary vasospasm, resulting in severe ST segment elevation, cardiac arrhythmias, and hemodynamic collapse (37,38), has been reported in patients as a consequence of calcium chloride administration to patients after cardiopulmonary bypass. Calcium may increase myocardial work by increasing ventricular contractility and increasing left and right ventricular afterload.

Indications for Calcium Administration

Calcium chloride administration may be indicated for selected patients after cardiopulmonary bypass, as in cardiopulmonary resuscitation, when either severe hyperkalemia or hypocalcemia is present. Modern cold, cardioplegic solutions contain high concentrations of potassium to provide asystolic cardiac arrest. During reperfusion, most of the intravascular potassium is washed out of the heart, but extracellular potassium concentrations within the myocardium may remain relatively high for many minutes thereafter, resulting in depression of cardiac conduction. Calcium may be needed to reverse this effect. In some cases, severe hypocalcemia may also occur during cardiopulmonary bypass. This phenomenon is certainly more common in children in whom hemodilution is more extreme and for whom blood products are more often included in the bypass pump priming solutions. Drop (39,40) has demonstrated, in both ischemic and nonischemic canine myocardium, that increases in ionized calcium from severely hypocalcemic levels to normal levels result in marked improvement in ventricular function as measured by changes in contractility (dP/dt). Milder degrees of hypocalcemia, which are commonly seen after cardiopulmonary bypass, were not evaluated.

Previous Human Surgical Studies of Epinephrine

We found low-dose epinephrine (30 $ng \cdot kg^{-1} \cdot min^{-1}$) to significantly increase cardiac index (14%) and mean arterial blood pressure (10%) without producing tachycardia. Other studies of epinephrine in cardiac surgery patients were performed after sternotomy but before bypass (41), immediately after emergence from bypass (42), or several hours after bypass in the intensive care unit (43,44). Piepenbrock et al. (41) compared relatively high doses of epinephrine (75 and 150 $ng \cdot kg^{-1} \cdot min^{-1}$) with dobutamine (2.5 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in 32 patients undergoing coronary artery bypass grafting. These drugs produced equivalent increases in heart rate; however, epinephrine produced greater increases in mean arterial blood pressure (16% and 27%), stroke volume index (26% and 37%), and cardiac index (47% and 69%) and a greater decrease in systemic vascular resistance (20% and 26%) at both study doses than dobutamine. Steen et al. (42) studied 34 patients having valve replacement or coronary artery grafting immediately after cessation of bypass. All patients had some evidence of left ventricular dysfunction. They compared epinephrine (40 $ng \cdot kg^{-1} \cdot min^{-1}$) with dopamine and dobutamine (5, 10, and 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Epinephrine increased cardiac index (30%), mean arterial blood pressure (27%), heart rate (11%), and left ventricular stroke work index (52%). These effects were comparable to those produced by 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine and dobutamine. Sato et al. (43) compared epinephrine (20, 40, and 80 $ng \cdot kg^{-1} \cdot min^{-1}$) with dobutamine (2, 4, and 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in 10 hemodynamically stable patients within 6 h of bypass. Epinephrine increased cardiac index (by 13.5%, 30.4%, and 34.8%) with the three doses, and decreased systemic vascular resistance (17.3%, 22.4%) and increased heart rate (8.7%, 14.0%) at the two higher doses. Dobutamine showed similar hemodynamic effects but with a greater increase in heart rate (23.3%) at the higher dose. Stephenson et al. (44) found in 24 patients recovering from various cardiac surgical procedures at equal inotropic doses of epinephrine (50 $ng \cdot kg^{-1} \cdot min^{-1}$) and dopamine (8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) that epinephrine increased heart rate (8%) less than dopamine (20%).

Calcium-Epinephrine Interaction

Our study also demonstrated no significant augmentation or inhibition of epinephrine's hemodynamic action by calcium chloride (5 mg/kg). Calcium is commonly added to epinephrine in an attempt to improve epinephrine's hemodynamic effects (45). Theoretically, as inotropes increase contractility by mobilizing intracellular calcium, additional calcium might improve the efficacy of inotropes, although this is unproven. Some investigators have reported that larger doses of calcium may actually inhibit the hemodynamic effects of catecholamines in animal studies (46–48). Recently, calcium was shown to attenuate dobutamine- and epinephrine-induced increases in cardiac index in patients recovering from cardiac surgery (17,18). Our failure to demonstrate a blunting effect of calcium chloride could reflect the smaller calcium dose (5 mg/kg) and the lower ionized calcium level we obtained. However, we believe 5 mg/kg of calcium, which still achieved a high-normal ionized calcium level, is a more appropriate clinical dose.

Study Limitations

Our study was limited to hemodynamically stable patients with good preoperative ventricular function; thus, the results may not apply to patients with poor preoperative or poor postbypass ventricular function. Feldman et al. (49) demonstrated that calcium, more so than β-receptor agonists, improved peak isometric contraction in isolated ventricular muscle strips from patients with end-stage heart failure. Unfortunately, calcium also prolonged the rate of diastolic relaxation; moreover, the tissue used in those studies was isolated from the effects of afterload, preload, heart rate, sympathetic stimulation, and coronary vascular tone. We attempted to control these variables in our study to minimize differences between groups by maintaining a constant preload with transfusion from the pump reservoir, by maintaining perfusion pressure above a safe clinical level with phenylephrine, and by maintaining a constant heart rate by temporary pacing. Phenylephrine is commonly administered in our institution immediately after bypass for significant vasodilation owing to our complete rewarming to 37°C and possibly owing to vasodilating metabolic substrates (glutamate and asparate) added to our cardioplegic solutions. Although phenylephrine was required in 23 of 40 patients, phenylephrine's use was equally distributed among the four patient groups; calculated systemic vascular resistance was not different among the groups; and comparison of patients receiving and not receiving phenylephrine revealed no significant hemodynamic differences within the calcium group.

We included patients receiving calcium blockers in our study to maintain its clinical relevance. Theoretically, calcium blockers may have altered some data, but there was equal distribution of calcium blocker therapy among comparable groups.

We studied hemodynamically stable patients with good ventricular function because we believed it unsafe to randomize patients with a high likelihood of requiring inotropic support after emergence from bypass to a placebo group. Without the placebo group, we could not have determined whether improvement in cardiac performance after calcium administration was related to a normal recovery mechanism (time dependent), as we found in this study, or to calcium administration per se as has been previously assumed. Without the placebo group, our data would suggest that calcium administration increases cardiac index. Some may argue that a higher dose of calcium (10–15 mg/kg) would have demonstrated cardiac output augmentation. However, comparable lack of effect on cardiac index was recently reported using a higher calcium chloride dose (50).

We conclude that calcium chloride administration (5 mg/kg) was similar to placebo at increasing cardiac index; moreover, there was no correlation between cardiac index and ionized calcium levels in hemodynamically stable patients after cardiopulmonary bypass. The cardiac index of coronary artery bypass patients improves with time after discontinuation of cardiopulmonary bypass without pharmacologic intervention. Calcium chloride does increase mean arterial blood pressure after cardiopulmonary bypass. Low-dose epinephrine (30 $ng \cdot kg^{-1} \cdot min^{-1}$) significantly increases both cardiac index and mean arterial blood pressure without producing tachycardia, whereas calcium neither augments nor inhibits the hemodynamic effects of low-dose epinephrine in these patients. Because of the association of intracellular calcium overload with myocardial ischemia and cell injury and the demonstrated lack of efficacy of calcium chloride at increasing cardiac index in this and many other studies, calcium chloride should not be administered after cardiopulmonary bypass for cardiac output augmentation in patients with good left ventricular function unless specifically indicated.

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References

1. Schaub MC, Kunz B. Regulation of contraction in cardiac and smooth muscles. J Cardiovasc Pharmacol 1986;8:S117–23.
2. Drop LJ. Ionized calcium, the heart, and hemodynamic function. Anesth Analg 1985;64:432–51.
3. Westhorpe RN, Varghese Z, Petrie A, Wills MR, Lumley J. Changes in ionized calcium and other plasma constituents associated with cardiopulmonary bypass. Br J Anaesth 1978; 50:951–7.
4. Drop LJ, Scheidegger D. Plasma ionized calcium concentration: important determinant of the hemodynamic response to calcium infusion. J Thorac Cardiovasc Surg 1980;79:425–31.
5. Urban P, Scheidegger D, Buchmann B, Skarvan K. The hemodynamic effects of heparin and their relation to ionized calcium levels. J Thorac Cardiovasc Surg 1986;91:303–6.
6. Kovalik SG, Ledgerwood AM, Lucas CE, Higgins RF. The cardiac effect of altered calcium homeostasis after albumin resuscitation. J Trauma 1981;21:275–9.
7. Robertie PG, Butterworth JF IV, Royster RL, et al. Normal parathyroid hormone responses to hypocalcemia during cardiopulmonary bypass. Anesthesiology 1991;75:43–8.
8. Shapira N, Schaff HV, White RD, Pluth JR. Hemodynamic effects of calcium chloride injection following cardiopulmonary bypass: response to bolus injection and continuous infusion. Ann Thorac Surg 1984;37:133–40.
9. Moffitt EA, Sethna DH, Gray RJ, Bussell J, Conklin CM, Matloff JM. Effects of calcium on the coronary and systemic circulation in patients after coronary surgery. Can Anaesth Soc J 1982;29:313–8.
10. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 1986;255: 2905–89.
11. Thompson BM, Steuven HS, Tonsfeldt DJ, et al. Calcium: limited indications, some danger. Circulation 1986;74(Suppl IV):90–3.
12. Stueven HA, Thompson BM, Aprahamian C, Tonsfeldt DJ. Calcium chloride: reassessment of use in asystole. Ann Emerg Med 1984;13:820–2.
13. Harrison EE, Amey BD. The use of calcium in cardiac resuscitation. Am J Emerg Med 1983;1:267–73.
14. Stueven HA, Thompson BM, Aprahamian C, Tonsfeldt DJ, Kastenson EH. Lack of effectiveness of calcium chloride in refractory asystole. Ann Emerg Med 1985;14:630–2.
15. Stueven HA, Thompson BM, Aprahamian C, Tonsfeldt DJ, Kastenson EH. The effectiveness of calcium chloride in refractory electromechanical dissociation. Ann Emerg Med 1985;14: 626–9.
16. Elz JS, Panagiotopoulos S, Nayler WG. Reperfusion-induced calcium gain after ischemia. Am J Cardiol 1989;63:7E–13E.
17. Butterworth JF IV, Zaloga GP, Prielipp RC, Tucker WY, Royster RL. Calcium inhibits the cardiac stimulating properties of dobutamine but not of amrinone. Chest (in press).
18. Zaloga GP, Strickland RA, Butterworth JF IV, Mark LJ, Mills SA, Lake CR. Calcium attenuates epinephrine's β-adrenergic effects in postoperative heart surgery patients. Circulation 1990;81:196–200.
19. Desai TK, Carlson RW, Thill-Baharozian M, Geheb MA. A direct relationship between ionized calcium and arterial pressure among patients in an intensive care unit. Crit Care Med 1988;16:578–82.
20. Bristow MR, Schwartz HD, Binetti G, Harrison DC, Daniels JR. Ionized calcium and the heart: elucidation of in vivo concentration-response relationships in the open-chest dog. Circ Res 1977;41:565–74.
21. Lang RM, Fellner SK, Neumann A, Bushinsky DA, Borow KM. Left ventricular contractility varies directly with blood ionized calcium. Ann Intern Med 1988;108:524–9.
22. Scheidegger D, Drop LJ, Schellenberg J-C. Role of the systemic vasculature in the hemodynamic response to changes in plasma ionized calcium. Arch Surg 1980;115:206–11.
23. Haddy FJ. Local effects of sodium, calcium and magnesium upon small and large blood vessels of the dog forelimb. Circ Res 1960;8:57–70.
24. Cork RC, Gallo JA Jr, Smith R, Copeland J. The systemic and pulmonary vascular effects of calcium in the post-op low cardiac output state. Anesth Analg 1988;67:S41.
25. Stanley TH, Isern-Amaral J, Liu WS, Lunn JK, Gentry S. Peripheral vascular versus direct cardiac effects of calcium. Anesthesiology 1976;45:46–58.
26. Denlinger JK, Kaplan JA, Lecky JH, Wollman H. Cardiovascular responses to calcium administered intravenously to man during halothane anesthesia. Anesthesiology 1975;42:390–7.
27. Auffant RA, Downs JB, Amick R. Ionized calcium concentration and cardiovascular function after cardiopulmonary bypass. Arch Surg 1981;116:1072–6.
28. Carlon GC, Howland WS, Kahn RC, Schweizer D. Calcium chloride administration in normocalcemic critically ill patients. Crit Care Med 1980;8:209–12.
29. Lappas DG, Drop LJ, Buckley MJ, Mundth ED, Laver MB. Hemodynamic response to calcium chloride during coronary artery surgery. Surg Forum 1975;26:234–5.
30. D'Hollander A, Primo G, Hennart D, Le Clerc JL, Deuvaert FE, Dubois-Primo J. Compared efficacy of dobutamine and dopa-

mine in association with calcium chloride on termination of cardiopulmonary bypass. J Thorac Cardiovasc Surg 1982;83:264–71.
31. Weisel RD, Mickle DAG, Finkle CD, Tumiati LC, Madonik MM, Ivanov J. Delayed myocardial metabolic recovery after blood cardioplegia. Ann Thorac Surg 1989;48:503–7.
32. Krause SM, Jacobus WE, Becker LC. Alterations in cardiac sarcoplasmic reticulum calcium transport in the postischemic "stunned" myocardium. Circ Res 1989;65:526–30.
33. Jennings RB, Ganote CE. Mitochondrial structure and function in acute myocardial ischemic injury. Circ Res 1976;38(Suppl I):I-80–91.
34. Przyklenk K, Patel B, Kloner RA. Diastolic abnormalities of post-ischemic "stunned" myocardium. Am J Cardiol 1987;60:1211–3.
35. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982;66:1146–9.
36. Kloner RA, Przyklenk K, Patel B. Altered myocardial states: the stunned and hibernating myocardium. Am J Med 1989;86(Suppl 1A):14–22.
37. Lemmer JH Jr, Kirsh MM. Coronary artery spasm following coronary artery surgery. Ann Thorac Surg 1988;46:108–15.
38. Boulanger M, Maillé JG, Pelletier GB, Michalk S. Vasospastic angina after calcium injection. Anesth Analg 1984;63:1124–6.
39. Drop LJ, Geffin GA, O'Keefe DD, et al. Relation between ionized calcium concentration and ventricular pump performance in the dog under hemodynamically controlled conditions. Am J Cardiol 1981;47:1041–51.
40. Geffin GA, Drop LJ, O'Keefe DD, et al. Global and regional function in the regionally ischaemic left ventricle related to plasma ionised calcium. Cardiovasc Res 1983;17:415–26.
41. Piepenbrock S, Reichelt W, Hempelmann G, Brackertz A, Dragojevic D, Hetzer R. Hemodynamic effects of dobutamine and epinephrine in patients during coronary surgery. Thorac Cardiovasc Surg 1979;27:378–85.
42. Steen PA, Tinker JH, Pluth JR, Barnhorst DA, Tarhan S. Efficacy of dopamine, dobutamine, and epinephrine during emergence from cardiopulmonary bypass in man. Circulation 1978;57:378–84.
43. Sato Y, Matsuzawa H, Eguchi S. Comparative study of effects of adrenaline, dobutamine, and dopamine on systemic hemodynamics and renal blood flow in patients following open heart surgery. Jpn Circ J 1982;46:1059–72.
44. Stephenson LW, Blackstone EH, Kouchoukos NT. Dopamine vs epinephrine in patients following cardiac surgery: randomized study. Surg Forum 1976;27:272–5.
45. Sladen RN. Management of the adult cardiac patient in the intensive care unit. In: Ream AK, Fogdall RP, eds. Acute cardiovascular management: anesthesia and intensive care. Philadelphia: JB Lippincott, 1982:481–548.
46. Zaloga GP, Willey S, Malcolm D, Chernow B, Holaday JW. Hypercalcemia attenuates blood pressure response to epinephrine. J Pharmacol Exp Ther 1988;247:949–52.
47. Prielipp RC, Hill T, Washburn D, Zaloga GP. Circulating calcium modulates adrenaline induced cyclic adenosine monophosphate production. Cardiovasc Res 1989;23:838–41.
48. Webb RC, Bohr DF. Mechanism of membrane stabilization by calcium in vascular smooth muscle. Am J Physiol 1978;235:C227–32.
49. Feldman MD, Copelas L, Gwathmey JK, et al. Deficient production of cyclic AMP: pharmacologic evidence of an important cause of contractile dysfunction in patients with end-stage heart failure. Circulation 1987;75:331–9.
50. Robertie PG, Johnston WE, Butterworth JF IV, Royster RL, Mills SA. Prospective, randomized trial of ephedrine, $CaCl_2$, and placebo in patients following cardiopulmonary bypass. Anesthesiology 1989;71:A1159.

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Influence of Anesthesia on the Threshold of Pacing-Induced Ischemia

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Increased myocardial oxygen demand, induced by increased heart rate, may cause myocardial ischemia in the presence of significant coronary artery disease. Alterations in anesthetic depth or technique might put at risk or protect myocardium with compromised blood flow. In 20 dogs with critical left anterior descending coronary artery (LAD) stenosis, atrial pacing rates from 100 to 160 beats/min were achieved, with end-tidal halothane 0.7% (LowH) and 1.1% (HighH), end-tidal isoflurane 1.1% (LowI) and 1.5% (HighI), as well as with continuous fentanyl plus midazolam (FM) infusion anesthesia. Despite significantly different mean arterial and coronary perfusion pressures, rate-pressure product, and left ventricular dP/dtmax, the pacing rate at which systolic shortening decreased below the lower limit of the physiologic response, indicating regional dysfunction, was the same in all investigated anesthesia conditions (LowH: 127 ± 4 beats/min; HighH: 128 ± 5 beats/min; LowI: 125 ± 4 beats/min; HighI: 122 ± 5 beats/min; FM: 124 ± 4 beats/min [mean ± SEM], $P > 0.05$). None of the investigated anesthesia conditions either increased ischemia tolerance or showed a detrimental effect on myocardium with compromised coronary blood flow.

(Anesth Analg 1992;74:14–25)

The effects of anesthesia on ischemic myocardium have been examined in many clinical and experimental studies, often with conflicting results. Halothane was first thought to be detrimental in the setting of myocardial ischemia (1); however, experimental studies demonstrated protection from ischemia in a total coronary occlusion model (2), increased tolerance of myocardium to ex vivo total ischemia (3), and increased coronary flow reserve (4) with the use of halothane. Further studies showed increased supply/demand ratios (5) and decreased infarct size (6) with halothane administration after left anterior descending coronary artery (LAD) occlusion in apical myocardium.

Isoflurane has been shown to benefit compromised myocardium. In a porcine model of critical LAD stenosis, isoflurane was shown to be more protective than halothane when compared by fatal to anesthetic ratios (7), and Tarnow et al. (8) demonstrated a higher threshold of pacing-induced ischemia with isoflurane anesthesia as compared with the awake state in patients with coronary artery disease (CAD).

Both isoflurane and halothane have also produced detrimental effects in compromised myocardium. Regional myocardial function deteriorated in the apical region supplied by a stenosed LAD when halothane or isoflurane concentrations were increased (9–11). Halothane was also shown to increase infarct size with LAD occlusion in rats (12), and isoflurane's potential to cause or potentiate coronary steal is well known (13). Halothane caused less regional dysfunction in compromised myocardium compared with isoflurane at similar hemodynamic end points, suggesting that halothane may have more protective, or less detrimental, effects on compromised myocardium (14).

Most of the previous investigations with myocardial ischemia involved a component of myocardial depression, such as the addition or increase in concentration of volatile anesthetics. One clinical study utilized the pacing-induced threshold of myocardial

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ischemia, with ischemia assessed by electrocardiographic or pulmonary artery occlusion pressure changes, as a measure of the protective effects of anesthesia (8). The present study sought to examine the effects of five different anesthetic regimens (fentanyl-midazolam infusions, 0.8 MAC and 1.2 MAC halothane, and 0.8 MAC and 1.2 MAC isoflurane) on the threshold of pacing-induced myocardial ischemia in a canine model of critical LAD stenosis (9,10,15, 16). The hypothesis was tested that different anesthetics or different depths of anesthesia provide a different degree of protection from ischemic dysfunction for myocardium with compromised coronary blood flow. Atrial pacing was chosen as a stress test because tachycardia repeatedly has been shown to be the only hemodynamic parameter significantly correlated with new intraoperative ischemia episodes and, by implication, with postoperative myocardial infarction in patients undergoing coronary artery bypass graft surgery (17–20).

Methods

This study was approved by the Institutional Animal Care and Use Committee, and all animals used in these experiments received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Science and published by the National Institutes of Health (NIH Publication No. 80-23, revised 1978).

Anesthesia Induction and Surgical Preparation

The present study represents a report on 20 successful experiments. Three animals did not complete the protocol, two owing to recurring endogenous pacemaker activity that prevented stable atrial pacing with 100 beats/min and one owing to the presence of some hemodynamic instability due to ongoing bleeding. In a fourth animal the LAD constriction inadvertently was manipulated during the study, and it became obvious at data analysis that coronary flow velocities considerably changed after this incident, and we therefore decided not to include this animal in data analysis. Anesthesia was induced in unpremedicated dogs, weighing 20–26 kg, with thiopental (15–25 mg/kg IV). The trachea was intubated and ventilation was begun with 100% oxygen to normocarbia at a rate of 10 breaths/min (Ohio V5 Airco, Ohmeda, Madison, Wis.). End-tidal carbon dioxide, halothane, and isoflurane concentrations were continuously measured by infrared spectroscopy (Datex model 254, Puritan Bennett Corporation, Wilmington, Mass.). During the surgical preparations, anesthesia was maintained with 1.0%–1.5% (end-tidal) halothane. The animals were placed in a right lateral position and an intravenous cannula was introduced in the hindlimb through which a continuous infusion of 0.9% saline ($3–4\ mL \cdot kg^{-1} \cdot h^{-1}$) was begun. A 7F pressure-transducer tipped catheter (Millar Instruments, Houston, Tex.) was inserted in the carotid artery and advanced to the aortic root, within 1 cm of the aortic valve, to obtain aortic pressure and arterial blood gas analyses.

The heart was exposed through a left thoracotomy and suspended in a pericardial cradle, and pacing wires were attached to the right atrium. The laterodorsal aspect of the right atrial wall at the confluence of the superior vena cava and the right atrium was then firmly compressed between the branches of an angled clamp to abolish sinus node activity. This procedure was started centrally, approximately one-third of the transverse diameter of the right atrium, and repeated every millimeter moving centripetally to the periphery of the right atrium; it was repeated until sinus node activity was abolished as evidenced by a junctional or occasionally a ventricular site taking over pacemaker activity, enabling stable atrial pacing at a frequency of 100 beats/min. When stable atrial pacing without interference between remaining (secondary) and artificial pacemaker activity was established, a test period of 30 min ensued to make sure that no pacemaker activity with a frequency higher than 100 beats/min recurred. A 5F pressure-transducer tipped catheter (Millar Instruments) was inserted into the left ventricle (LV) through a stab incision at the apex of the heart to measure LV pressure. The fat pad was dissected off the aortic root, and an appropriately sized 5-MHz Doppler ultrasonic flow probe was placed around the aortic root, and aortic blood flow velocity was measured via a Doppler flowmeter (model 100-1000-05, Triton Technologies, San Diego, Calif.). A proximal segment of the LAD was dissected free and a 10-MHz Doppler flow probe was placed around the LAD, and LAD blood flow velocity was measured with a second Doppler flow meter (model 100-1000-10, Triton Technologies) (Figure 1).

A pair of ultrasonic crystals (diameter 1.5–2 mm), oriented in the short axis of the heart, were placed in the apical region of the heart in the territory supplied by the LAD (Figure 1). The regional myocardial contraction pattern was assessed by continuously measuring the segment length between the two sonomicrometer crystals, based on the measurement of ultrasonic transit time (Sonomicrometer; model 120, Triton Technologies) (21,22). The correct placement of the LAD crystals within the area of ischemia was confirmed by observing regional function during a

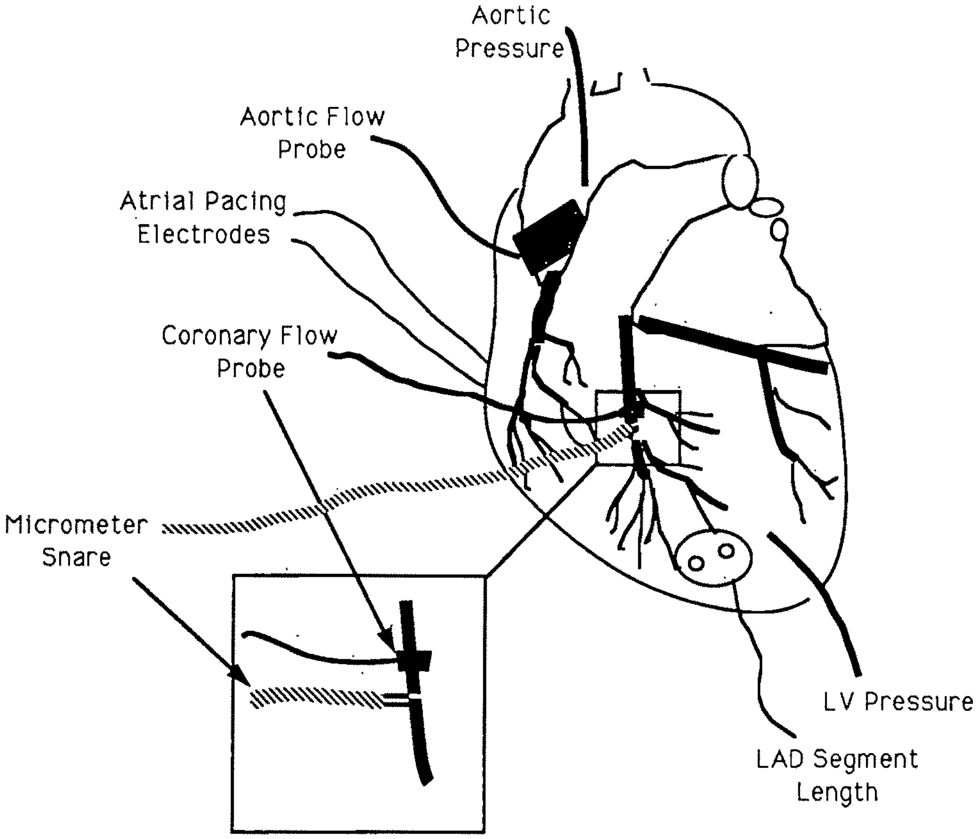

Figure 1. Experimental preparation.

brief LAD occlusion. The occurrence of an ischemic contraction pattern (see below) not only confirmed proper crystal placement in the LAD territory but also the absence of significant collateralization (15).

Experimental Protocol

After completion of the surgical preparations, inspiratory oxygen concentration was changed to 50% (in nitrogen), halothane was adjusted to 0.9% end-tidal concentration, and a stabilization period ensued, during which all measurement devices were calibrated. Baseline measurements and the physiologic hyperemic response to a 10-s total LAD occlusion were recorded at a pacing rate of 100 beats/min. At the same pacing rate, critical constriction of the LAD was then imposed by slowly tightening a micrometer-controlled snare to the point where the hyperemic response to a 10-s total LAD occlusion was totally abolished, yet no dysfunction occurred in the LAD-supplied territory (9). With the critical constriction stable for 30 min, a second set of measurements (critical constriction) was recorded at a pacing rate of 100 beats/min.

Anesthesia was then changed in random order to 0.7% and 1.1% end-tidal halothane and 1.1% and 1.5% end-tidal isoflurane. A 30-min period between changes in anesthesia technique before data collection ensured steady-state end-tidal concentration (infrared analysis) as well as steady-state hemodynamics. During this time blood gases were analyzed, ventilation was adjusted, and bicarbonate was given, when base excess was less than −5 mEq/L. Within each of these four anesthesia conditions, a first set of measurements was made at a pacing rate of 100 beats/min. In 5-min intervals heart rate was increased in steps of 10 beats/min until distinct ischemic dysfunction occurred in the LAD territory, as evidenced by a greater than 20% decrease in systolic shortening from systolic shortening at a pacing rate of 100 beats/min, or an increase in postsystolic shortening by more than 20% from postsystolic shortening at a pacing rate of 100 beats/min (with the same anesthetic). The highest pacing rate used in the present study was 160 beats/min (Figure 2).

At each pacing level one set of measurements was recorded. After having recorded the measurements at the highest pacing level, the pacing rate was reduced to 100 beats/min and anesthesia was changed to the next anesthesia condition. A 30-min period was al-

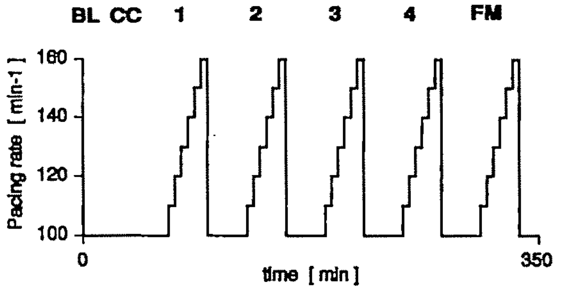

Figure 2. Experimental protocol with pacing rates at the different experimental stages. BL = baseline, CC = critical constriction, 1–4 = pacing epochs with 0.7% and 1.1% end-tidal halothane and 1.1% and 1.5% isoflurane performed in random order, and FM = fentanyl-midazolam.

lowed for recovery from ischemia (23), during which blood gas analyses were performed and ventilation was adjusted or bicarbonate given, as appropriate. After having completed all measurements in all of these four anesthesia types, fentanyl-midazolam intravenous anesthesia was begun with two initial boluses of fentanyl (5 μg/kg) and two initial boluses of midazolam (50 μg/kg), amounting to total bolus doses of 10 μg/kg for fentanyl and 100 μg/kg for midazolam. The time interval from one bolus to the next was approximately 3 min. These initial boluses were followed by continuous infusions (fentanyl: 0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, midazolam: 1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The infusion rates of fentanyl and midazolam were constant throughout a 30-min period before as well as during the pacing protocol with fentanyl-midazolam, which was performed identically as that described for volatile anesthetics. No further boluses of fentanyl or midazolam were administered during the constant fentanyl and midazolam infusions. To investigate the effects of the volatile anesthetics on the threshold of pacing-induced ischemia without residual fentanyl or midazolam, the fentanyl-midazolam pacing portion of the anesthetic protocol was always performed last.

Data Processing and Calculations

The pressure signals were amplified by a low-noise DC pre-amplifier (Grass Instruments, Quincy, Mass.), digitally converted (analog-digital converter, model 16AF, MetraByte Corporation, Taunton, Mass.), and recorded with a personal computer (model Deskpro 386/20, Compaq, Computer Corporation, Houston, Tex.) at a sampling rate of 500 Hz over a period of 10 s. The LV pressure–LAD segment length loop was displayed continuously in real time; characteristic alterations indicative of ischemia (24) were used to determine ischemic end points of pacing (see below).

Stroke volume was obtained as the product of the perfused cross-sectional area of the aortic flow probe and the systolic aortic blood flow velocity time integral, and cardiac output was computed as the product of stroke volume and heart rate. Left ventricular dP/dt, the first derivative of LV pressure, was determined as the instantaneous slope of the LV pressure-time curve. End-diastole was defined by the first consistent positive deflection of LV dP/dt, and end-systole by the abrupt cessation of forward blood flow in the aortic root, indicating aortic valve closure.

Derived cardiovascular parameters were computed according to standard formulas. Systemic vascular resistance (SVR) ($dyne \cdot s \cdot cm^{-5}$) was computed as

$$SVR = MAP \times 80/CO,$$

where MAP is the mean arterial blood pressure (mm Hg) and CO is the cardiac output (L/min) (25).

The end-diastolic segment length and end-systolic length were determined using the above definitions for end-diastole and end-systole. Systolic shortening (SS) and postsystolic shortening (PSS) were calculated as (16,22)

$$SS = [(EDL - LminS)/EDL] \times 100,$$

$$PSS = [(LminS - LminD)/(EDL - LminD)] \times 100,$$

where EDL is the end-diastolic segment length, LminS is the minimum length obtained during systole, and LminD is the minimum length obtained during early diastole. For subsequent statistical analyses, negative values for PSS were listed as zero (26).

Definition of Dysfunctional Contraction Pattern

To define the physiologic reaction of SS of the apical LV region to increasing pacing rates, an additional seven animals without critical coronary constriction underwent the same protocol (see experimental protocol) and served as controls. The physiologic reaction of SS for each anesthetic was determined for pacing rates between 100 and 160 beats/min (Figure 3A). At each pacing rate, the physiologic range for SS was defined as mean ± 2 SD (Figure 3B).

After having shown with a repeated-measures analysis of variance (see below) that control animals without LAD stenosis and animals with LAD stenosis reacted significantly differently to increasing pacing rates, a dysfunctional apical contraction pattern was defined in animals with critical LAD constriction as any SS below the lower limit of the physiologic range (Figure 4). This analysis was performed after the study was completed. The heart rate at which the contraction pattern of the LAD territory first became dysfunctional was designated as the threshold of pacing-induced ischemia.

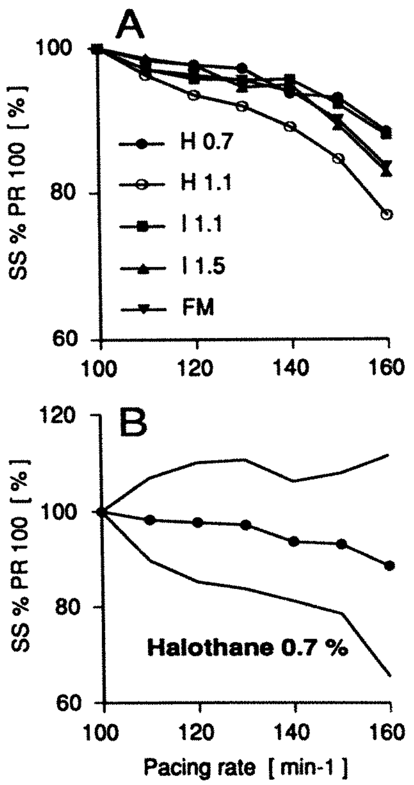

Figure 3. Physiologic reaction of the apical LV region to increasing pacing rates in dogs without LAD stenosis. **A**. Systolic shortening at pacing rates of 100–160 beats/min normalized to SS at a pacing rate of 100 beats/min (SS% PR100) with 0.7% (H 0.7) and 1.1% (H 1.1) end-tidal halothane, 1.1% (I 1.1) and 1.5% (I 1.5) isoflurane, as well as fentanyl-midazolam (FM). **B**. Physiologic range of SS normalized to SS at a pacing rate of 100 beats/min (SS% PR100) at pacing rates of 100–160 beats/min, defined as mean ± 2 SD, with 0.7% end-tidal halothane.

Statistics

Data analysis used in the present study represents a three-stage procedure.

First stage. Because the pacing rates could not be randomized with the present experimental protocol in which the pacing rate was increased until distinct LAD contractile dysfunction occurred, there will be some serial correlation between pacing rates. Thus data were analyzed in a multivariate manner. Each hemodynamic response to increasing pacing rates was considered a seven-component multivariate response vector, and repeated-measures analysis of variance ("REPEATED" statement in PROC GLM, SAS, Version 6.04, SAS Institute, Cary, N.C.) was used to test for differences between experimental groups (control animals without LAD constriction, and animals with LAD constriction), among anesthetic conditions, and to test for group-pacing rate and anesthetic condition-pacing rate interactions (27).

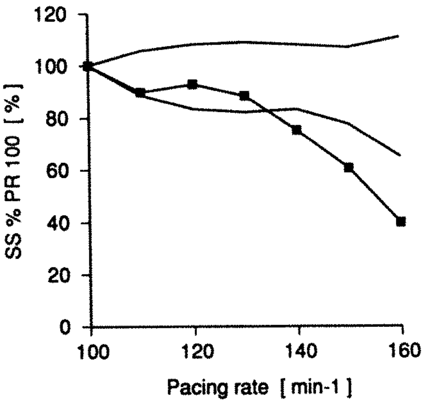

Figure 4. Representative example (with 1.1% end-tidal isoflurane) in a dog where at a pacing rate of 140 beats/min, SS of the LAD territory (normalized to SS at a pacing rate of 100 beats/min) (SS% PR100) decreased below the lower limit of the physiologic range for dogs without LAD stenosis; accordingly the threshold of pacing-induced ischemia in this dog was 140 beats/min with 1.1% end-tidal isoflurane.

The group-pacing rate interaction tests for differences between groups over the various pacing rates. A nonsignificant group-pacing rate interaction term implies that the control group (without LAD constriction) and the animals with LAD stenosis behave similarly (in a parallel manner) over the pacing rates investigated. This interaction term therefore represents an overall test of the effect of critical LAD constriction. The anesthetic condition-pacing rate interaction term tests for differences among the anesthetic conditions over the pacing rates investigated. A nonsignificant anesthetic condition-pacing rate interaction term implies that the responses to various pacing rates are similar among the anesthetic conditions tested in the present study. No individual comparison tests were used in this first stage of data analysis.

Second stage. In some animals with LAD stenosis the pacing rate could not be increased up to a maximum heart rate of 160 beats/min because of severe LAD contractile dysfunction (incomplete multivariate response vector), and such pacing epochs thus had to be excluded from the repeated-measures multivariate analysis of variance. The threshold of pacing-induced ischemia therefore was additionally determined for each anesthetic condition in every individual dog as outlined above (see definition of dysfunctional contraction pattern).

Third stage. Data at a pacing rate of 100 beats/min and the threshold of pacing-induced ischemia were compared by repeated-measures analysis of variance. If the anesthetic effect was significant, then the individual marginal means were compared using Fisher's unprotected least-significant difference test. A probability level of $P < 0.05$ was considered significant. Data are presented as mean ± SEM. Paired t-tests were used to compare global cardiovascular and regional cardiac function between baseline and critical constriction.

Results

The group-pacing rate interaction was significant for all global cardiovascular and regional myocardial function parameters, except cardiac output, indicating that the control animals without LAD stenosis and animals with LAD stenosis responded differently to increasing pacing rates. The three-way interaction of pacing rate-group-anesthetic condition was not significant for any global cardiovascular or regional cardiac function parameter, which implies that within the groups (control animals without LAD stenosis or animals with LAD stenosis) the anesthetic condition had no effect on the response of hemodynamic variables to increasing pacing rates. Because pacing epochs in which pacing rate could not be increased up to a maximum heart rate of 160 beats/min (owing to severe LAD contractile dysfunction in animals with LAD stenosis) could not be included in the repeated-measures multivariate analysis of variance, the threshold of pacing-induced ischemia was additionally determined for each anesthetic condition in every individual dog to characterize global cardiovascular and regional myocardial function at a pacing rate of 100 beats/min and at the threshold of pacing-induced ischemia. Results of this separate comparison are outlined in Tables 2–4.

Sixteen of 20 animals consistently showed dysfunctional contraction patterns above a certain pacing rate in all investigated anesthesia conditions. In four animals, a normal (i.e., noncompromised coronary flow) contractile pattern was observed with increasing pacing rates despite critical LAD constriction. As no dysfunctional contraction pattern could be induced in these animals, the comparison between global cardiovascular and regional myocardial functions at a pacing rate of 100 beats/min and the threshold of pacing-induced ischemia are based on those 16 animals, which consistently showed a dysfunctional contraction pattern above a certain pacing rate. In these 16 animals, two pacing epochs could not be analyzed: one fentanyl-midazolam epoch caused by a sudden total LAD occlusion, documented by a sudden absence of LAD blood flow velocity with resultant cessation of SS independent of pacing rate, and one fentanyl-midazolam epoch caused by technical difficulties with the sonomicrometer. In one pacing epoch with 1.1% halothane, in one with 1.1% isoflurane, and in one with fentanyl-midazolam, the LAD territory showed no dysfunctional contraction pattern at any pacing rate; therefore, these three pacing epochs were excluded from the comparison between the global cardiovascular and regional cardiac functions at a pacing rate of 100 beats/min and the threshold of pacing-induced ischemia.

Table 1. Hemodynamic and Cardiac Function Parameters

	Baseline	Critical constriction
n	16	16
HR (beats/min)	101 ± 1	101 ± 0
MAP (mm Hg)	83.4 ± 4.2	84.2 ± 3.7
LVEDP (mm Hg)	7.0 ± 0.5	6.8 ± 0.6
CPP (mm Hg)	66.5 ± 4.2	67.6 ± 3.8
+dP/dtmax (mm Hg/s)	1118 ± 57	1129 ± 63
−dP/dtmax (mm Hg/s)	−1143 ± 54	−1132 ± 69
SV (mL)	24.7 ± 1.7	24.0 ± 2.0
CO (L/min)	2.5 ± 0.2	2.4 ± 0.2
SVR (dyne·s·cm^{-5})	2857 ± 235	3046 ± 244
RPP (mm Hg/min × 10^{-2})	94 ± 4	95 ± 4
EDL (mm)	12.3 ± 1.2	12.2 ± 1.1
SS (%)	22.4 ± 2.7	21.8 ± 2.9
PSS (%)	5.9 ± 1.9	10.2 ± 2.7

HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; CPP, coronary perfusion pressure; +dP/dtmax, maximum positive dP/dt; −dP/dtmax, maximum negative dP/dt; SV, stroke volume, CO, cardiac output; SVR, systemic vascular resistance; RPP, systolic rate-pressure product; EDL, end-diastolic segment length; SS, systolic shortening; PSS, postsystolic shortening.

Baseline Versus Critical Constriction

Hemodynamic parameters as well as global and regional myocardial functions were unchanged by imposing a critical coronary constriction (Table 1).

Hemodynamic Data and Left Ventricular Function at a Pacing Rate of 100 beats/min

At a pacing rate of 100 beats/min, there were the expected differences in mean arterial and coronary perfusion pressures, maximum positive and negative dP/dt, systemic vascular resistance, and systolic rate-pressure product between the investigated anesthetics (Table 2).

Threshold of Pacing-Induced Ischemia

The threshold of pacing-induced ischemia was not different between the anesthesia conditions investigated in the present study (Figure 5). The median heart rate at which LAD contractile dysfunction first occurred was 120 beats/min (110, 140; lower and upper quartiles) for 0.7% end-tidal halothane, 130 beats/min (110, 140) for 1.1% end-tidal halothane, 120

Table 2. Hemodynamic Data at a Pacing Rate of 100 beats/min

	Halothane		Isoflurane		
	0.7%	1.1%	1.1%	1.5%	FM
n	16	15	15	16	13
HR (beats/min)	100 ± 0	100 ± 1	101 ± 1	100 ± 0	101 ± 0
MAP (mm Hg)	82.8 ± 4.0^{b,d}	71.7 ± 3.0^{a,e}	77.8 ± 3.2^{d}	70.8 ± 1.7^{a,c,e}	81.9 ± 4.6^{b,d}
LVEDP (mm Hg)	5.9 ± 0.7	6.2 ± 0.7	5.7 ± 0.7	5.7 ± 0.6	5.7 ± 1.0
CPP (mm Hg)	67.0 ± 3.9^{b,d}	56.7 ± 3.0^{a,e}	61.6 ± 3.4^{d}	56.3 ± 2.0^{a,c,e}	66.8 ± 4.6^{b,d}
+dP/dtmax (mm Hg/s)	1163 ± 91^{b,d,e}	941 ± 59^{a,c,e}	1149 ± 68^{b,d,e}	993 ± 66^{a,c,e}	1261 ± 89^{a,b,c,d}
−dP/dtmax (mm Hg/s)	−1037 ± 92^{b,d}	−852 ± 59^{a,c}	−1034 ± 81^{b,d}	−872 ± 54^{a,c}	−953 ± 76
SV (mL)	24.1 ± 1.5	23.1 ± 1.9	23.6 ± 1.1	25.3 ± 1.5	23.3 ± 1.5
CO (L/min)	2.4 ± 0.2	2.3 ± 0.2	2.4 ± 0.1	2.5 ± 0.1	2.3 ± 0.2
SVR (dyne·s·cm^{-5})	2912 ± 218^{d}	2637 ± 180	2720 ± 183^{d}	2373 ± 171^{a,c,e}	2934 ± 235^{d}
RPP (mm Hg/min × 10^{-2})	92 ± 4^{b,d}	81 ± 3^{a,c,e}	90 ± 3^{b,d}	80 ± 2^{a,c,e}	92 ± 5^{b,d}
Coronary flow velocity (cm/s)	13.7 ± 2.0	11.7 ± 2.1	14.0 ± 1.9	12.2 ± 1.8	14.9 ± 2.1

FM, fentanyl-midazolam; HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; CPP, coronary perfusion pressure; +dP/dtmax, maximum positive dP/dt; −dP/dtmax, maximum negative dP/dt; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance; RPP, systolic rate-pressure product.

Values are mean ± SEM.

[a] Significantly different ($P < 0.05$) from 0.7% halothane.

[b] Significantly different ($P < 0.05$) from 1.1% halothane.

[c] Significantly different ($P < 0.05$) from 1.1% isoflurane.

[d] Significantly different ($P < 0.05$) from 1.5% isoflurane.

[e] Significantly different ($P < 0.05$) from fentanyl-midazolam.

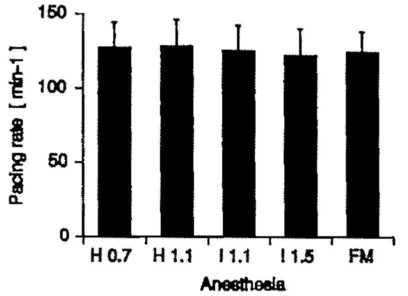

Figure 5. Threshold of pacing-induced ischemia with 0.7% (H 0.7) and 1.1% (H 1.1) end-tidal halothane, 1.1% (I 1.1) and 1.5% (I 1.5) isoflurane, as well as fentanyl-midazolam (FM). Note that there is no difference in the threshold of pacing-induced ischemia between these five anesthesia conditions.

beats/min (110, 140) for 1.1% end-tidal isoflurane, 110 beats/min (110, 130) for 1.5% end-tidal isoflurane, and 120 beats/min (110, 130) for fentanyl-midazolam.

Hemodynamic Data and Left Ventricular Function at Threshold of Pacing-Induced Ischemia

The same parameters that were different between the investigated anesthesia conditions at a pacing rate of 100 beats/min were also different between the investigated anesthesia conditions at the threshold of pacing-induced ischemia except stroke volume. Increasing the heart rate to the threshold of pacing-induced ischemia caused an increase in the systolic rate-pressure product and, with most anesthetics, a decrease in stroke volume, an increase in cardiac output, and a decrease in systemic vascular resistance (Table 3). Coronary perfusion pressure, however, was unchanged as compared with a pacing rate of 100 beats/min regardless of anesthetic technique. Mean arterial pressure and left ventricular end diastolic pressure (LVEDP) also were unchanged; the only exceptions were that mean arterial pressure decreased by 5.1 ± 6.8 mm Hg with 1.1% halothane, and LVEDP increased by 1.4 ± 2.1 mm Hg with 0.7% halothane and ischemia. Maximum positive dP/dt was unchanged by pacing-induced ischemia in all anesthesia conditions; maximum negative dP/dt decreased with 1.1% halothane and with fentanyl-midazolam but was otherwise unchanged at the threshold of pacing-induced ischemia as compared with a pacing rate of 100 beats/min.

Contraction Pattern of the Left Anterior Descending Coronary Artery Territory

There was no difference in SS or PSS between the investigated anesthesia conditions, neither at a pacing rate of 100 beats/min nor at the threshold of pacing-induced ischemia. End-diastolic length with fentanyl-midazolam was slightly but statistically significantly smaller than the end-diastolic length with volatile anesthetics at both experimental stages (Table 4). Increasing the heart rate to the threshold of pacing-induced ischemia caused a decrease in SS; PSS increased at the threshold of pacing-induced ischemia with all anesthetic techniques except for fentanyl-midazolam, which may be due to a large variabil-

Table 3. Hemodynamic and Coronary Flow Data at the Threshold of Pacing-Induced Ischemia

	Halothane		Isoflurane		
	0.7%	1.1%	1.1%	1.5%	FM
n	16	15	15	16	13
HR (beats/min)	**127 ± 4**	**128 ± 5**	**125 ± 4**	**122 ± 5**	**124 ± 4**
MAP (mm Hg)	79.8 ± 4.5^{b,d}	**66.6 ± 3.0**^{a,c,e}	79.5 ± 3.6^{b,d}	71.1 ± 2.3^{a,c}	78.2 ± 4.0^{b}
LVEDP (mm Hg)	**7.3 ± 0.9**	7.2 ± 0.8	5.8 ± 0.6	6.4 ± 0.6	7.0 ± 1.1
CPP (mm Hg)	64.9 ± 4.2^{b,d}	53.2 ± 3.2^{a,c,e}	64.7 ± 3.5^{b,d}	56.7 ± 2.7^{a,c}	63.7 ± 4.0^{b}
+dP/dtmax (mm Hg/s)	1107 ± 83^{b,d}	893 ± 62^{a,c,d,e}	1164 ± 80^{b,d}	992 ± 50^{a,b,c,e}	1125 ± 82^{b,d}
−dP/dtmax (mm Hg/s)	−975 ± 107^{b}	**−772 ± 66**^{a,c}	−1057 ± 108^{b,d,e}	−844 ± 62^{c}	**−820 ± 77**^{c}
SV (mL)	**20.1 ± 1.8**^{c,d}	**20.5 ± 1.4**	23.2 ± 1.5^{a,e}	**22.9 ± 1.2**^{a,e}	**19.7 ± 1.5**^{c,d}
CO (L/min)	2.6 ± 0.3	**2.6 ± 0.2**	**2.9 ± 0.3**	**2.8 ± 0.2**	2.4 ± 0.2
SVR (dyne·s·cm^{-5})	3099 ± 573^{b,d}	**2143 ± 138**^{a}	**2402 ± 226**	**2189 ± 177**^{a}	**2751 ± 221**
RPP (mm Hg/min × 10^{-2})	**111 ± 7**^{b,d}	**94 ± 5**^{a,c,e}	**111 ± 6**^{b,d}	**97 ± 4**^{a,c}	**107 ± 6**^{b}
Coronary flow velocity (cm/s)	13.6 ± 2.0^{b}	10.8 ± 2.1^{a,c,e}	14.4 ± 1.9^{b,d}	12.4 ± 1.8^{c}	14.9 ± 2.1^{b}

FM, fentanyl-midazolam; HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; CPP, coronary perfusion pressure; +dP/dtmax, maximum positive dP/dt; −dP/dtmax, maximum negative dP/dt; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance; RPP, systolic rate-pressure product.

Values are mean ± SEM. Boldface indicates significantly different ($P < 0.05$) from value at a pacing rate of 100 beats/min (Table 2).

[a] Significantly different ($P < 0.05$) from 0.7% halothane.

[b] Significantly different ($P < 0.05$) from 1.1% halothane.

[c] Significantly different ($P < 0.05$) from 1.1% isoflurane.

[d] Significantly different ($P < 0.05$) from 1.5% isoflurane.

[e] Significantly different ($P < 0.05$) from fentanyl-midazolam.

Table 4. Contraction Pattern of the Left Anterior Descending Coronary Artery Territory

	Halothane		Isoflurane		
	0.7%	1.1%	1.1%	1.5%	FM
At a pacing rate of 100 beats/min					
n	16	15	15	16	13
HR (beats/min)	100 ± 0	100 ± 1	101 ± 1	100 ± 1	101 ± 0
EDL (mm)	11.8 ± 1.3^{e}	12.1 ± 1.1^{e}	11.5 ± 1.3^{e}	11.8 ± 1.2^{e}	9.3 ± 0.8^{a,b,c,d}
SS (%)	22.2 ± 3.2	20.0 ± 3.0	19.7 ± 2.9	19.6 ± 2.9	18.6 ± 3.4
PSS (%)	8.7 ± 2.7	13.5 ± 3.1	13.6 ± 3.6	15.8 ± 4.0	12.4 ± 4.9
At the threshold of pacing-induced ischemia					
n	16	15	15	16	13
HR (beats/min)	**127 ± 4**	**128 ± 5**	**125 ± 4**	**122 ± 5**	**124 ± 4**
EDL (mm)	**11.1 ± 1.3**^{e}	11.8 ± 1.3^{e}	11.3 ± 1.4^{e}	11.5 ± 1.3^{e}	9.1 ± 0.9^{a,b,c,d}
SS (%)	**16.1 ± 2.1**	**13.8 ± 2.5**	**15.3 ± 2.5**	**14.8 ± 2.5**	**13.0 ± 2.3**
PSS (%)	**12.7 ± 3.4**	**21.0 ± 4.9**	**18.4 ± 4.5**	**22.2 ± 5.3**	17.5 ± 6.1

FM, fentanyl-midazolam; HR, heart rate; MAP, mean arterial pressure; EDL, end-diastolic segment length; SS, systolic shortening; PSS, postsystolic shortening.

Values are mean ± SEM. Boldface indicates significantly different ($P < 0.05$) from value at a pacing rate of 100 beats/min (Table 2).

[a] Significantly different ($P < 0.05$) from 0.7% halothane.

[b] Significantly different ($P < 0.05$) from 1.1% halothane.

[c] Significantly different ($P < 0.05$) from 1.1% isoflurane.

[d] Significantly different ($P < 0.05$) from 1.5% isoflurane.

[e] Significantly different ($P < 0.05$) from fentanyl-midazolam.

ity in the data (Table 4). End-diastolic length was unchanged by the increase in heart rate, except for a slight decrease during 0.7% halothane (Table 4).

Discussion

The results of the present study demonstrate that the threshold of pacing-induced ischemia is not different between the anesthesia conditions investigated in the present study. The reaction of the contraction pattern of LV myocardium supplied by a compromised coronary artery to increasing heart rates, therefore, is not influenced by type (halothane, isoflurane, or fentanyl plus midazolam) or depth of anesthesia.

Critique of Methodology

Canine model of coronary pathophysiology. There is a rich net of coronary collaterals, both in normal human as well as normal dog hearts. These collaterals, however, differ in that human coronary collaterals, although undisputably present in subepicardial LV myocardium, are mainly concentrated in subendocardium, whereas the dog's coronary collaterals are preferentially located subepicardially and may be somewhat larger in diameter than native human coronary collaterals (28,29). In patients with CAD, however, collateralization increases considerably, depending on severity of coronary obstruction, time-course of development of coronary obstruction, and probably other individual factors (28). These CAD-related human coronary collaterals are transmurally distributed, with maximum density in subendocardial myocardium; their size may be considerably increased compared with native coronary collaterals (28). Differences in collateral distribution and size of collaterals between dogs and humans therefore are reduced by adaptive changes of the human coronary circulation owing to CAD. Further, most studies of cardiovascular and coronary physiology have been performed in dogs, and so comparability with previous results is certainly best with a dog model. In contrast, normal pigs only rarely show important coronary collateralization (30), and therefore may be less suitable for studies of cardiac function and coronary physiology with respect to the particular situation in humans with CAD, although coronary collaterals can be induced in pigs by slowly obstructing large coronary vessels over several weeks by the Ameroid-constrictor method (30). This collateralization is somewhat unpredictable in that some pigs will develop collateral vessels; in others, however, only few collaterals were detectable weeks after Ameroid-constrictor implantation (30). Additionally, a relatively high percentage of loss of animals occurs (29,30). Based on these considerations the acute canine model was chosen.

Pacing range of 100–160 beats/min. Heart rates of conscious dogs are relatively variable, with values between 80 and 120 beats/min reported (31–38). With volatile anesthetics, heart rates between 100 and 125 beats/min are frequently observed (6,9–11,16,25, 26,39); heart rates considerably above this range, however, are typically found in barbiturate or α-chloralose-urethane–anesthetized dogs (2,5,22,40). As the present study investigates the question of whether different anesthetics result in a different threshold of pacing-induced ischemia, the investigation had to be performed during anesthesia; and because the secondary pacemaker centers that became active after having crushed the sinus node typically had a frequency of 80–90 per minute, atrial pacing at 100 beats/min was the lowest stable pacing rate at which *all* dogs could be paced. We therefore chose atrial pacing starting with a frequency of 100 beats/min as the most physiologic procedure in anesthetized dogs, although this baseline pacing frequency may be slightly higher than the control heart rate in some studies in conscious dogs. We were, however, not interested per se in mimicking conscious-state physiology, but rather wished to create an anesthetized state with physiology comparable to previously reported studies. If a different pacing rate would have been used to impose the critical LAD constriction, LAD contractile dysfunction may have occurred at a different pacing rate than the one at which LAD contractile dysfunction actually did occur in the present study. We were, however, not primarily interested in the pacing rate at which LAD contractile dysfunction occurs, but rather in the difference between the above rate and the pacing rate used to impose critical constriction.

Rapid atrial pacing. Rapid atrial pacing increases myocardial oxygen consumption (41–43), which in turn leads to a considerable increase in myocardial perfusion in hearts with unobstructed coronary arteries (44). With a critical coronary constriction, however, reserve coronary vasodilation has already been used to compensate for coronary stenosis and consequently no adequate increase in myocardial blood flow is possible to offset the oxygen demand induced by atrial pacing, thus inducing regional ischemia (38,40). Rapid atrial pacing, therefore, represents a procedure by which a dysbalance between oxygen delivery and oxygen demand can reliably be induced in myocardium with compromised coronary blood flow. Although angina pectoris occurs within 45 s in CAD patients paced at supracritical rates (45), an interval of 5 min was chosen to increase the pacing rate to achieve a steady state of ischemia at each experimental stage (46).

Randomization of sequence of anesthetics. To investigate the effects of volatile anesthetics on the threshold of pacing-induced ischemia without residual fentanyl or midazolam, the fentanyl-midazolam pacing epoch was performed last and could not be included in randomization. The randomization compensated for potential effects of time and/or repeated ischemic episodes; however, because fentanyl-midazolam anesthesia was not randomized, such effects might have biased the comparisons with volatile anesthesia. If the effects of time or repeated ischemic episodes influence the reaction of the contraction pattern to increasing pacing rates, this influence would be expected to be most obvious in a comparison between the first pacing epoch, irrespective of anesthetic condition, and the fentanyl-midazolam pacing epoch. The threshold of pacing-induced ischemia therefore was specifically analyzed with respect to the experiment sequence. The heart rate at which a dysfunctional contraction pattern first occurred was found to be the same at all experimental stages. The same was true for individual comparisons between the fentanyl-midazolam epoch and previous pacing epochs. This finding is consistent with a previous report showing that the threshold of pacing-induced ischemia is the same in successive pacing epochs using a continuous pacing protocol (23). The fact that the threshold of pacing-induced ischemia indeed was the same at the final fentanyl-midazolam pacing epoch as in the directly preceding pacing epoch ($P > 0.40$) as well as in the first pacing epoch ($P > 0.40$) is evidence that the effects of time and/or previous ischemic episodes are relatively minor, if at all present, and the fentanyl-midazolam pacing epochs therefore were included in the overall analysis.

Statistics. Multiple statistical analyses were used to evaluate differences seen with increasing pacing rates and with anesthetic techniques. Initially, repeated-measures multivariate analysis of variance was used to detect differences between experimental groups (control animals without LAD constriction and animals with LAD constriction) and among anesthetic conditions; additionally, group-pacing rate and anesthetic condition-pacing rate interactions were tested. The finding of a significant group-pacing rate interaction demonstrated that animals without LAD constriction reacted differently to increasing pacing rates than animals with LAD stenosis. The finding of a nonsignificant anesthetic condition-pacing rate interaction indicated that the responses to increasing pacing rates were similar with all anesthetic conditions tested in the present study. Determination of the threshold of pacing-induced regional myocardial ischemia, however, involved additional data analyses. One problem was inherent to the study. Individual animal variability meant that each animal could become ischemic at a specific pacing rate, and not all animals with critical LAD stenosis could complete the pacing protocol to the maximum pacing rate of 160 beats/min without the possibility of significant irreversible regional myocardial dysfunction. We therefore halted the pacing protocol if distinct ischemic regional dysfunction occurred, as evidenced by characteristic morphologic changes in the pressure–length loop during real time (24). We later analyzed these data for each animal using rigidly defined criteria with respect to SS based on findings in control animals without LAD stenosis (Figures 3 and 4). This methodology allowed us to precisely determine global cardiovascular and regional myocardial function at the threshold of pacing-induced ischemia with all anesthetic techniques. The three-stage data analysis used in the present study therefore represents an effective way of analyzing all available data, yet focusing on those results that are physiologically important.

Influence of Anesthetics on the Threshold of Pacing-Induced Ischemia

Based on findings suggesting a cardioprotective potential of halothane or isoflurane (2–8), a higher threshold of pacing-induced ischemia for these volatile anesthetics than with fentanyl-midazolam might be expected. On the other hand, from reports of detrimental effects of halothane and isoflurane on compromised myocardium (9–12) we might have expected particularly low thresholds of pacing-induced ischemia with halothane and isoflurane. Actually, neither expectation was fulfilled in the present study. How can this be explained? In those studies showing a cardioprotective effect of halothane such as a reduction of sum of ST elevation (2), a decrease in infarct size (6), or an improved regional balance between oxygen supply and oxygen demand due to total LAD occlusion (5), halothane decreased a relatively high baseline heart rate considerably but only mildly depressed mean arterial and coronary perfusion pressures, thus influencing the balance between oxygen delivery and cardiac oxygen consumption favorably. Detrimental effects of halothane or isoflurane, however, were reported in studies in which these volatile anesthetics depressed mean arterial and coronary perfusion pressures considerably, thus compromising coronary perfusion (9–12,14). This may be particularly unfavorable with isoflurane because heart rate tends to increase with isoflurane (11,13,14). The balance between hemodynamic factors favoring coronary perfusion and factors affecting myocardial oxygen consumption on the other hand thus seems to be more important in terms of function and integrity of compromised LV myocardium than the specific anesthetic used to create the particular hemodynamic condition.

Our finding that the threshold of pacing-induced ischemia with isoflurane was similar to the one found with halothane or fentanyl-midazolam anesthesia is difficult to compare with the report of Tarnow et al. (8), which demonstrated an improved tolerance to pacing-induced myocardial ischemia with isoflurane anesthesia in patients with CAD before coronary artery bypass surgery. Tarnow et al. compared the threshold of pacing-induced ischemia, as evidenced by changes in electrocardiogram and pulmonary capillary wedge pressure, in the awake patient and the patient anesthetized with isoflurane and nitrous oxide. Thus not only isoflurane but also the change from the awake to the anesthetized state per se could have been responsible for the improved tolerance to pacing. Mean arterial pressure during isoflurane anesthesia was lower as compared with the awake state, and the rate-pressure product at any given heart rate thus also was lower during isoflurane anesthesia. If we assume a lower rate-pressure product indicates lower myocardial oxygen consumption (47), then the improved tolerance to increasing pacing rates could also be explained on a hemodynamic basis.

Coronary steal is a mechanism by which collateral flow-dependent areas of the heart might have been compromised by isoflurane (7,11,13,39). The fact that the threshold of pacing-induced ischemia was not lower with isoflurane than with halothane or fentanyl-midazolam indicates that isoflurane-induced coronary steal was not significant in the present study. This does not exclude the possibility that isoflurane-induced coronary steal might be significant with a more steal-prone coronary anatomy (13). The concept of isoflurane-induced coronary steal, however, has recently been seriously challenged, because no selective redistribution of coronary flow away from collateral-dependent myocardium was found in a maximally steal-prone multivessel CAD dog model, a model with a "positive control," in which adenosine did induce significant coronary steal (39). The decrease in myocardial perfusion during isoflurane was rather due to an isoflurane-induced decrease in mean arterial and coronary perfusion pressures; and these pressures were remarkably similar among the investigated anesthetics in the present study, confirming the conclusion that isoflurane's action on general hemodynamics and in particular on mean arterial and coronary perfusion pressures may be more important with respect to myocardial perfusion than specific coronary vasodilation with the potential of coronary steal in collateral flow-dependent areas.

Four dogs consistently did not develop regional ischemia with increasing pacing rate with all investigated anesthesia conditions despite critical LAD constriction. In brief, total LAD occlusions were performed before the experiments to test proper placement of the sonomicrometer crystals in the LAD territory; however, these four dogs also exhibited distinctly ischemic contraction patterns within a few seconds. Therefore, no immediately available collaterals were thought present. The possibility, however, that some collateral blood supply was recruited within each pacing run over time in these four animals cannot be excluded. Individual dogs either consistently showed normal reactions to increasing pacing rates (4 of 20 dogs) with all anesthetic conditions or consistently exhibited dysfunctional contraction patterns in the LAD territory above a certain pacing rate (16 of 20 dogs). In the latter animals exhibiting myocardial dysfunction, the threshold of pacing-induced ischemia was found to be identical in all investigated anesthesia conditions.

The finding of the present study that the threshold of pacing-induced ischemia is neither influenced by the type (halothane, isoflurane, fentanyl-midazolam) nor the depth of anesthesia (0.8 MAC and 1.2 MAC, respectively) corresponds with the results of large clinical studies in patients with CAD undergoing coronary artery bypass surgery (20,48), showing that outcome is not influenced by anesthetic technique. New ischemic episodes before cardiopulmonary bypass, the quality of the distal anastomoses, and ischemic time during aortic cross-clamping but not the anesthetic technique were correlated with postoperative myocardial infarction (20). Tachycardia was the only hemodynamic parameter that occurred significantly more often in those patients with new ischemic episodes; periods of hypotension or hypertension were not significant (20). The lack of influence of the anesthetic technique on outcome in these patients has been explained by the fact that the extent and severity of each patient's CAD, as well as the speed and quality of the surgical revascularization, are more important factors determining overall outcome than the anesthetic used (20,48). The present study demonstrates that there is no difference in the threshold of pacing-induced ischemia between halothane, isoflurane, and fentanyl-midazolam in a physiologically controlled model of CAD. Therefore, avoiding tachycardia may be of major importance in providing anesthesia for patients with CAD; the choice of a specific anesthetic agent, however, seems to be of less concern.

In summary, the effect of anesthetics on the threshold of pacing-induced ischemia was investigated in 20 dogs with a critical LAD constriction. The heart rate at which a dysfunctional contraction pattern in the LAD territory occurred was identical at all investigated anesthesia conditions (0.7% and 1.1% halothane, 1.1% and 1.5% isoflurane, fentanyl-midazolam). The reaction of the contraction pattern of LV myocardium supplied by a compromised coronary artery to increasing heart rates therefore seems neither to be influenced by type nor depth of anesthesia.

References

1. Hamilton WK. Do let the blood pressure drop and do use myocardial depressants. Anesthesiology 1976;45:273–4.
2. Bland JHL, Lowenstein E. Halothane induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 1976;45:287–93.
3. Pollard JB, Hill RF, Lowe JE, et al. Myocardial tolerance to total ischemia in the dog anesthetized with halothane or isoflurane. Anesthesiology 1988;69:17–23.
4. Verrier ED, Edelist G, Consigny M, Robinson S, Hoffman JIE. Greater coronary vascular reserve in dogs anesthetized with halothane. Anesthesiology 1980;53:445–59.
5. Smith G, Rogers K, Thorburn J. Halothane improves the

balance of oxygen supply to demand in acute experimental myocardial ischemia. Br J Anaesth 1980;52:577–83.

6. Davis RF, DeBoer LWV, Rude RE, Lowenstein E, Maroko PR. The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occlusion. Anesthesiology 1983;59:402–11.
7. Roberts SL, Gilbert M, Tinker JH. Isoflurane has a greater margin of safety than halothane in swine with and without major surgery or critical coronary stenosis. Anesth Analg 1987;66:485–91.
8. Tarnow J, Markschiess-Hornung A, Schulte-Sasse U. Isoflurane improves the tolerance to pacing-induced myocardial ischemia. Anesthesiology 1986;64:147–56.
9. Lowenstein E, Foëx P, Francis M, Davies WL, Yusuf S, Ryder WA. Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentration in the dog. Anesthesiology 1981;55:349–59.
10. Francis CM, Foëx P, Lowenstein E, et al. Interaction between regional myocardial ischemia and left ventricular performance under halothane anesthesia. Br J Anaesth 1982;54:965–79.
11. Priebe HJ, Foëx P. Isoflurane causes regional myocardial dysfunction in dogs with critical coronary artery stenoses. Anesthesiology 1987;66:293–300.
12. Kissin I, Stanbridge R, Bishop SP, Reves JG. Effect of halothane on myocardial infarct size in rats. Can Anaesth Soc J 1981;28:239–43.
13. Priebe HJ. Isoflurane and coronary hemodynamics. Anesthesiology 1989;71:960–76.
14. Priebe HJ. Isoflurane causes more severe regional myocardial dysfunction than halothane in dogs with a critical coronary stenosis. Anesthesiology 1988;69:72–83.
15. Leone BJ, Philbin DM, Lehot JJ, Foëx P, Ryder WA. Gradual or abrupt nitrous oxide administration in a canine model of critical coronary stenosis induces regional myocardial dysfunction that is worsened by halothane. Anesth Analg 1988;67:814–22.
16. Leone BJ, Lehot JJ, Francis CM, Cutfield GR, Foëx P. Beta-blockade reverses regional dysfunction in ischemic myocardium. Anesth Analg 1987;66:607–14.
17. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.
18. Slogoff S, Keats AS. Further observations on perioperative myocardial ischemia. Anesthesiology 1986;65:539–42.
19. Slogoff S, Keats AS. Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 1988;68:676–80.
20. Slogoff S, Keats AS. Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 1989;70:179–88.
21. Bugge-Asperheim B, Leraand S, Kiil F. Local dimensional changes of the myocardium measured by ultrasonic technique. Scand J Clin Lab Invest 1969;24:361–71.
22. Theroux P, Franklin D, Ross J Jr, Kemper WS. Regional myocardial function during acute coronary artery occlusion and its modification by pharmacological agents in the dog. Circ Res 1974;35:896–906.
23. Thadani U, Lewis JR, Mathew TM, West RO, Parker JO. Reproducibility of clinical and hemodynamic parameters during pacing stress testing in patients with angina pectoris. Circulation 1979;60:1036–44.
24. Foëx P, Francis CM, Cutfield GR, Leone BJ. The pressure-length loop. Br J Anaesth 1988;60:65S–71S.
25. Bernard JM, Wouters PF, Doursout MF, Florence B, Chelly JE, Merin RG. Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Anesthesiology 1990;72:659–62.
26. Priebe HJ. Myocardial ischemia in a canine model of pulmonary hypertension and right coronary artery stenosis. Anesthesiology 1990;72:517–25.
27. Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley & Sons, 1986:220–40.
28. Fulton WFM. The coronary arteries. Arteriography, microanatomy, and pathogenesis of obliterative coronary artery disease. Springfield: Charles C. Thomas, 1965.
29. Schaper W, Jageneau A, Xhonneux R. The development of collateral circulation in the pig and dog heart. Cardiologia 1967;51:321–35.
30. Blumgart HL, Zoll PM, Freedberg AS, Gilligan DR. The experimental production of intercoronary arterial anastomoses and their functional significance. Circulation 1950;1:10–27.
31. Theroux P, Ross J, Franklin D, Kemper WS, Sasayama S. Regional myocardial function in the conscious dog during acute coronary occlusion and responses to morphine, propranolol, nitroglycerin and lidocaine. Circulation 1976;53:302–14.
32. Vatner SF, Baig H, Manders WT, Ochs H, Pagani M. Effects of propranolol on regional myocardial function, electrograms, and blood flow in conscious dogs with myocardial ischemia. J Clin Invest 1977;60:353–60.
33. Vatner SF. Correlation between acute reductions in myocardial blood flow and function in conscious dogs. Circ Res 1980;47:201–7.
34. Amano J, Thomas JX, Lavallee M, et al. Effects of myocardial ischemia on regional function and stiffness in conscious dogs. Am J Physiol 1987;252:H110–7.
35. Glower DD, Spratt JA, Kabas JS, Davis JW, Rankin JS. Quantification of regional myocardial dysfunction after acute ischemic injury. Am J Physiol 1988;255:H85–93.
36. Canty JM. Coronary pressure-function and steady-state pressure-flow relations during autoregulation in the unanesthetized dog. Circ Res 1988;63:821–36.
37. Roan PG, Buja LM, Izquierdo C, Hashimi H, Saffer S, Willerson JT. Interrelationship between regional left ventricular function, coronary blood flow, and myocardial necrosis during initial 24 hours and 1 week after experimental coronary occlusion in awake, unsedated dogs. Circ Res 1981;49:31–40.
38. Neill WA, Oxendine JM, Phelps NC, Anderson RP. Subendocardial ischemia provoked by tachycardia in conscious dogs with coronary stenosis. Am J Cardiol 1975;35:30–6.
39. Hartman JC, Kampine JP, Schmelling WT, Warltier DC. Steal-prone coronary circulation in chronically instrumented dogs: isoflurane versus adenosine. Anesthesiology 1991;74:744–56.
40. O'Riordan JB, Flaherty JT, Khuri SF, Brawley RK, Pitt B, Gott VL. Effects of atrial pacing on regional myocardial gas tensions with critical coronary stenosis. Am J Physiol 1977;232:H49–53.
41. Boerth RC, Covell JW, Pool PE, Ross J. Increased myocardial oxygen consumption and contractile state associated with increased heart rate in dogs. Circ Res 1969;24:725–34.
42. Kralios AC, Tsagaris TJ, Kuida H. Comparison of rhythm and rate-induced myocardial O_2 consumption changes before and after coronary occlusion. Am Heart J 1978;96:372–80.
43. Rooke GA, Feigl EO. Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. Circ Res 1982;50:273–86.
44. Neill WA, Phelps NC, Oxendine JM, Mahler DJ, Sim DN. Effect of heart rate on coronary blood flow distribution in dogs. Am J Cardiol 1973;32:306–12.
45. Sowton GE, Balcon R, Cross D, Frick MH. Measurement of the angina threshold using atrial pacing. A new technique for the study of angina pectoris. Cardiovasc Res 1967;1:301–7.
46. Watanabe I, Johnson TA, Buchanan J, Engele CL, Gettes LS. Effect of graded coronary flow reduction on ionic, electrical and mechanical indexes of ischemia in the pig. Circulation 1987;76:1127–34.
47. Kitamura K, Jorgensen CR, Gobel FL, Taylor HL, Wang Y. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol 1972;32:516–22.
48. Tuman KJ, McCarthy RJ, Spiess BD, DaValle M, Dabir R, Ivankovich AD. Does choice of anesthetic agent significantly affect outcome after coronary artery bypass surgery? Anesthesiology 1989;70:189–98.

Electrocardiographic R-Wave Changes During Cardiac Surgery

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The diagnostic accuracy of exercise electrocardiography has been improved by incorporation of R-wave gain factor to correct the measured ST-segment changes. If marked changes in R-wave amplitude occur in individual patients during cardiac operations, a similar gain factor correction may improve the intraoperative diagnosis of myocardial ischemia. This investigation was designed to determine the frequency and magnitude of intraoperative V_5 R-wave amplitude changes during cardiac operations. Electrocardiograms were recorded from 83 patients while patients were awake, anesthetized (baseline), after placement of the Favaloro and Canadian sternal retractors, and at end-operation. Compared with baseline values, placement of the Canadian sternal retractor was associated with a reduction in V_5 R-wave amplitude from 15 ± 1 to 10 ± 1 mm (mean ± SEM), in V_5 S-wave amplitude from 3.5 ± 0.4 to 1.7 ± 0.3 mm, and in absolute ST-segment deviation from 0.50 ± 0.04 to 0.39 ± 0.05 mm. Changes in V_5 R-wave amplitude were correlated with changes in ST-segment deviation in patients with baseline ST-segment deviations ≥0.5 mm ($r = 0.55$, $P = 0.0004$, $n = 37$). Changes associated with the Favaloro retractor and the respiratory cycle were less marked. However, the V_5 R-wave amplitude was decreased from 15 ± 1 to 9 ± 1 mm at end-operation. In conclusion, sternal spreading with the Canadian retractor was associated with marked reductions in V_5 R- and S-wave amplitudes and ST-segment deviations. Marked changes in V_5 R-wave amplitude persisted after sternal closure. These results support the proposal that inclusion of an R-wave gain factor may improve perioperative electrocardiographic monitoring.

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Electrocardiographic (ECG) monitoring of ST-segment depression or elevation is the most common means for diagnosing intraoperative myocardial ischemia. Despite use of the most sensitive leads (1,2) and the introduction of on-line computer-assisted ST-segment analysis (3), ECG monitoring remains imperfect. For example, many ischemic episodes detectable by transesophageal echocardiography are not accompanied by diagnostic ECG changes (4–6).

Efforts to improve the diagnostic accuracy of ECG ST-segment measurement during treadmill exercise testing have included measurement of R-wave amplitude (RWA). Several investigators (7–9) have shown that the magnitude of ST depression observed during exercise depends in part on RWA. In addition, when an R-wave gain factor correction is applied to individuals with abnormally small or large V_5 RWAs, the corrected ST depression improves as a predictor of myocardial ischemia (9).

Some patients demonstrate dramatic changes in V_5 RWA during the course of cardiac surgery, particularly after placement of the sternal retractor (Figure 1). As RWA correction improves the diagnostic accuracy of the electrocardiogram during treadmill exercise testing, it may also improve the accuracy of intraoperative ECG monitoring. Therefore, this study was designed to determine the frequency and magnitude of V_5 RWA changes associated with placement of the Favaloro and Canadian sternal retractors during cardiac operations. In addition, as computer-aided monitoring of small (0.1 mm) ST-segment changes was performed in all patients, we examined the relationship between changes in V_5 RWAs and ST changes in individual patients.

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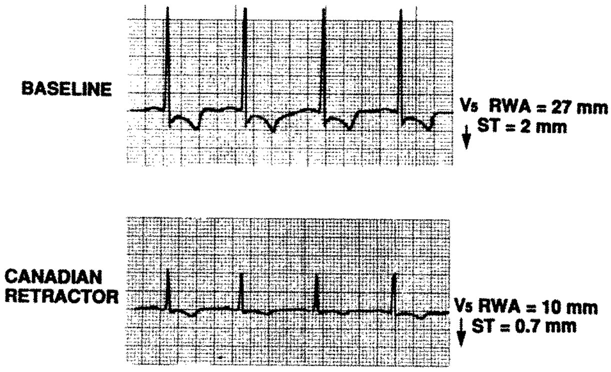

Figure 1. Change in electrocardiogram after placement of Canadian sternal retractor. Reduction in V_5 R-wave amplitude (RWA) is accompanied by a comparable reduction in ST-segment depression (↓ ST). In both tracings, 10 mm = 1 mV.

Methods

Study Subjects

Eighty-three patients undergoing cardiac operations through a median sternotomy were studied. The protocol was approved by the Human Subjects Committee of the Brigham and Women's Hospital. Fifty patients were male and 33 were female. Their body weights ranged from 40 to 118 kg (mean 74 ± 15 kg), and heights ranged from 145 to 185 cm (mean 170 ± 10 cm). The surgical procedure was coronary artery bypass grafting (CABG) in 54, reoperation CABG in 5, valve repair or replacement in 17, reoperation valve replacement in 1, combined valve replacement/CABG in 5, and ventricular myomectomy in 1. Twenty-seven patients had a preoperative diagnosis of left ventricular hypertrophy (LVH) by standard ECG or echocardiographic criteria. Four patients had atrial fibrillation, one had junctional rhythm, and the remainder were in sinus rhythm. None had bundle branch block.

Electrocardiographic Monitoring and Data Recording

The electrocardiograms were recorded with a Marquette 7010RA bedside monitor (Marquette Electronics, Inc., Milwaukee, Wis.) and a Marquette S7100 Direct Digital Writer. Five silver/silver chloride disposable electrode pads were attached to each patient: the arm electrodes were placed behind each humeral head, leg electrodes at the lateral aspect of the iliac crests, and the precordial electrode in the V_5 position in the anterior axillary line lateral to V_4 (10).

Leads I, II, III, and V_5 were recorded simultaneously at a paper speed of 25 mm/s, through a filter bandwidth of 0.05–105 Hz, and a gain setting of 10 mm/mV (or 5 mm/mV in 10 patients when RWA exceeded the recorder range). At least 10 beats or two full respiratory cycles were recorded at the following times: (1) awake, before induction of anesthesia; (2) baseline, after anesthetic induction and tracheal intubation but before incision; (3) Favaloro, after sternotomy during maximal sternal lifting with the Favaloro retractor; (4) Canadian, during maximal sternal spreading with the Canadian retractor but before cardiopulmonary bypass; and (5) end operation, before leaving the operating room. At time 1, recordings were made during spontaneous ventilation. At time 2, separate recordings were made during positive-pressure ventilation and during sustained end-expiration. At times 3, 4, and 5, recordings were made during sustained end-expiration.

A Favaloro retractor (Pilling, Fort Washington, Pa.) was used to facilitate dissection of the internal mammary artery. Consequently, it was used in 62 of 64 patients having CABG surgery. A Canadian retractor (Codman, Randolph, Mass.) was used in all 83 patients.

Values for heart rate (HR), mean arterial blood pressure (MAP), and computer-aided measurement of ST-segment displacement were determined at the time of each ECG recording. The ST-segment displacement was measured 60 ms after QRS offset and compared with an isoelectric point 40 ms before QRS onset. The digital value of ST-segment elevation (positive) or depression (negative), measured to the nearest 0.1 mm (0.01 mV), was recorded automatically by the computer and visually confirmed by an investigator and a research nurse, both of whom reviewed all the ECG paper tracings.

Data Analysis

R-wave and S-wave amplitudes (SWA) were measured to the nearest 1 mm (0.1 mV) in each lead (I, II, III, V_5) by visual inspection of the paper recordings. Recordings at one-half standard gain (5 mm/mV) were measured and corrected so that all data were analyzed and reported at standard gain (10 mm/mV). The QRS axes were calculated by hand using limb lead RWA, SWA, and standard graphic methods (11). Reported values are mean ± SEM. All values for RWA, SWA, and ST segments are reported in millimeters.

Preliminary analysis of the six measured variables (V_5 RWA, V_5 SWA, ST deviation, QRS axis, HR, MAP) showed some to be normally distributed whereas others were slightly skewed. To apply a uniform test of statistical probability to each of these measures, subjects were categorized according to whether they showed increases or decreases (relative to baseline) in the given variable after retractor placement or at end-operation. The McNemar χ^2 test was

Table 1. Electrocardiographic and Hemodynamic Changes During Favaloro and Canadian Retractor Placement

Variable	Measurement	Mean ± SEM	Total *n*	*n* Increase	*n* Decrease	χ^2	*P*
V_5 RWA (mm)	Baseline	15.1 ± 0.8	83				
	Favaloro	13.7 ± 0.8	62				
	Canadian	9.9 ± 0.7	83				
	ΔFavaloro		62	30	22	0.94	0.50
	ΔCanadian		83	9	69	44.6	0.001
V_5 SWA (mm)	Baseline	3.5 ± 0.4	83				
	Favaloro	2.2 ± 0.3	62				
	Canadian	1.7 ± 0.3	83				
	ΔFavaloro		62	12	28	5.63	0.02
	ΔCanadian		83	3	59	48.8	0.001
V_5 ST-ABS (mm)	Baseline	0.50 ± 0.04	83				
	Favaloro	0.45 ± 0.04	61[a]				
	Canadian	0.39 ± 0.05	82[a]				
	ΔFavaloro		61[a]	31	22	1.21	0.30
	ΔCanadian		82[a]	20	51	12.68	0.001
QRS axis (degrees)	Baseline	38.5 ± 4.5	83				
	Favaloro	39.3 ± 5.1	62				
	Canadian	40.2 ± 5.0	83				
	ΔFavaloro		62	27	27	0.01	0.99
	ΔCanadian		83	44	33	1.30	0.30
Heart rate (beats/min)	Baseline	64 ± 2	83				
	Favaloro	61 ± 1	62				
	Canadian	68 ± 2	83				
	ΔFavaloro		62	31	27	0.16	0.70
	ΔCanadian		83	46	29	3.41	0.10
Mean arterial pressure (mm Hg)	Baseline	75 ± 1	83				
	Favaloro	79 ± 1	62				
	Canadian	76 ± 1	83				
	ΔFavaloro		62	38	21	4.34	0.05
	ΔCanadian		83	44	38	0.30	0.70

RWA, R-wave amplitude; SWA, S-wave amplitude; ST-ABS, absolute value of ST displacement; ΔFavaloro, change between baseline and Favaloro retractor; ΔCanadian, change between baseline and Canadian retractor; Total *n*, total number of subjects or comparisons; *n*-Increase, number of subjects showing increase; *n*-Decrease, number of subjects showing decrease; χ^2, McNemar χ^2 value comparing *n*-increase and *n*-decrease.

[a] Missing value of ST-ABS in one patient due to technical equipment problem.

then applied to determine the significance of these changes. Repeated-measures analysis of variance (ANOVA) was used to test the interaction between LVH or type of operation and the changes in V_5 RWA caused by placement of the sternal retractor.

Results

The mean values for V_5 RWA were 15 ± 1, 14 ± 1, and 10 ± 1 mm during baseline, Favaloro retraction, and Canadian retraction, respectively (Table 1). In 32 of 62 patients (52%), Favaloro retractor placement was associated with a change in V_5 RWA greater than 2 mm. However, V_5 RWAs were equally likely to increase or decrease in magnitude (Table 1, Figure 2, upper panel). In contrast, 63 of 83 patients (76%) showed a change in V_5 RWA of greater than 2 mm with placement of the Canadian retractor; of these, 61 of 63 (97%) showed reduction of V_5 RWA (Figure 2, middle panel). Overall, 42 of 83 patients (51%) showed a 5-mm or greater reduction in V_5 RWA after placement of the Canadian retractor (Figure 2, middle panel).

Other changes associated with placement of the Canadian retractor included a reduction in V_5 SWA from 3.5 ± 0.4 to 1.7 ± 0.3 mm and a decrease in absolute amount of ST-segment elevation or depression from 0.50 ± 0.04 to 0.39 ± 0.05 mm (Table 1). No significant changes occurred in QRS axis (39 ± 5° to 40 ± 5°), HR (64 ± 2 to 68 ± 2 beats/min), or MAP (75 ± 1 to 76 ± 1 mm Hg).

Thirty-seven subjects whose postinduction baseline ST-segments showed at least 0.5-mm elevation or depression and whose ST-segments did not change sign (depression to elevation or vice versa) after the Canadian retractor placement were selected for further analysis. In these patients, changes in the absolute amount of ST-segment deviation associated with the Canadian retractor were compared with changes in V_5 RWA; Pearson correlation analysis showed a significant linear relation between these two variables ($r = 0.55$, $P = 0.0004$ [Figure 3]).

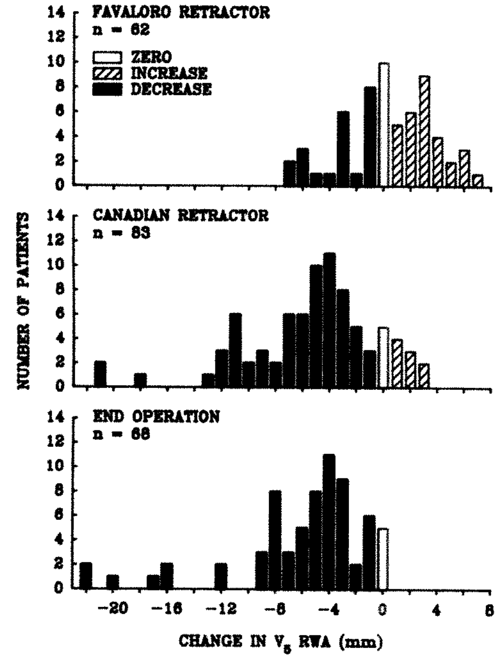

Figure 2. Change in V_5 R-wave amplitude (RWA) after placement of Favaloro sternal retractor (*upper panel*), Canadian sternal retractor (*middle panel*), and at end-operation (*lower panel*) compared with baseline values after anesthetic induction.

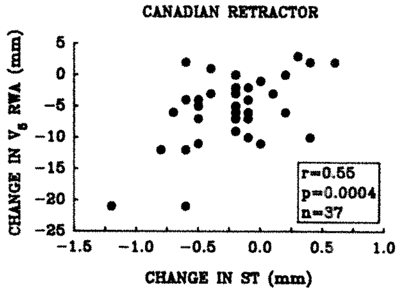

Figure 3. Scatterplot relating changes in V_5 R-wave amplitude (RWA) to changes in absolute amount of V_5 ST-segment deviation.

The 27 patients with LVH had larger V_5 RWAs than those without LVH, both at the postinduction baseline (20 ± 2 vs 13 ± 1 mm, $P \leq 0.001$) and after placement of the Canadian retractor (15 ± 2 vs 8 ± 0.4 mm, $P \leq 0.001$). Regardless of whether LVH was present, the Canadian retractor was associated with a similar reduction in V_5 RWA ($P = 0.639$, ANOVA).

Nineteen patients had operations other than CABG. These patients had larger V_5 RWAs at baseline (22 ± 2 vs 13 ± 1 mm, $P \leq 0.001$) and with the Canadian retractor (17 ± 2 vs 8 ± 0.4 mm, $P \leq 0.001$) compared with patients undergoing CABG. Reduction in V_5 RWA associated with the Canadian retractor was not influenced by type of operation ($P = 0.644$, ANOVA).

The effects of both spontaneous and positive pressure ventilation on V_5 RWAs were determined in each patient while the chest was closed. Rather than attempt to precisely identify peak inspiration and end expiration, we recorded the electrocardiogram over two complete respiratory cycles, and maximum and minimum V_5 RWAs were noted. During spontaneous ventilation, 5% of patients had greater than 2-mm variation in V_5 RWA over the course of the respiratory cycle. In contrast, during positive pressure ventilation, 38% of patients had greater than 2-mm variation in V_5 RWA.

At end-operation, ECG recordings were available in 68 patients. In the remaining 15, cardiac pacing or hemodynamic instability precluded study measurements. In 55 of 68 patients (81%), V_5 RWA was reduced more than 2 mm compared with postinduction baseline values (Figure 2, lower panel). Overall, V_5 RWA was reduced from 15 ± 1 to 9 ± 1 mm. No patient showed an increase in V_5 RWA at end-operation, whereas 63 showed a decrease ($\chi^2 = 61.0$, $P \leq 0.001$).

Discussion

The most noteworthy observation in this study was that placement of the Canadian sternal retractor was associated with ECG changes during cardiac operations. Sternal spreading by this retractor reduced V_5 RWA by one-third and V_5 SWA by one-half, whereas QRS frontal plane axis remained unchanged. Taken together, these results suggest that the V_5 QRS complex generally "shrinks" after placement of the Canadian retractor.

We hypothesized that a reduction in V_5 RWA during Canadian retraction should be associated with a reduction in the relative amount of ST displacement if the shrinkage phenomenon affected the entire ECG complex. Using computer-aided monitoring techniques, we were able to detect small changes in the ST segment (3,12). Our data showed that ST displacement decreased 22% during retraction, with a strong correlation between changes in V_5 RWAs and ST displacements within individual patients (Figure 3). These observations suggest that proper interpretation of intraoperative ST elevation or depression should consider the associated RWA; ST changes that accompany RWA changes simply may reflect shrinkage or magnification of the entire ECG complex.

The importance of considering RWA when interpreting ST changes during treadmill exercise has been emphasized by several investigators. Hakki et al. (8) studied 81 patients with documented coronary artery disease and identified small baseline V_5 RWA (≤11 mm) as a determinant of failure to develop ST depression during exercise. Only 2 of 26 patients with small R waves had positive exercise electrocardiograms despite having multivessel coronary artery disease. Hollenberg et al. (9,13) developed a computer-derived treadmill exercise score, which adjusts the magnitude of ST depression to a standardized RWA (12 mm in V_5 and 8 mm in aVF). Use of the RWA correction in patients with particularly small ($\leq$9 mm) or large ($\geq$17 mm) R waves improved prediction of ischemia, as compared with a thallium exercise score (9). Furthermore, application of the R-wave gain correction in a low-risk population of 377 asymptomatic young men allowed the exercise electrocardiogram to offer markedly improved specificity, reducing the number of positive scores from 45 to 3 (13).

Each of these studies compared RWAs across groups of patients. In contrast, using an approach more like our own, Gerson et al. (7) analyzed RWA changes within individual subjects during exercise testing. Using bipolar leads CC_5 and aVL in 100 volunteers, these authors found a significant relation between RWA and magnitude of ST depression, with correlation coefficients ranging between 0.28 and 0.56 depending on the ECG lead and stage of exercise.

This degree of correlation is similar to that observed in our patients during Canadian retractor placement. It is likely that improved sensitivity and specificity of intraoperative ST-segment monitoring would be achieved when changes in RWA occurring during operation are detected and an adjustment or gain correction applied. Clearly, this approach to ST monitoring using RWA gain correction must be validated with an independent means for monitoring intraoperative myocardial ischemia.

Our data suggest that ECG RWA and ST changes after placement of the Canadian retractor were not solely the result of myocardial ischemia. Although nonhemodynamically mediated myocardial ischemia is extremely common in this patient population (14–16), the rapid development of these ECG changes immediately after retractor placement, which are unassociated with changes in HR or MAP, make an ischemic etiology less likely. However, only 30% (r = 0.55) of the variability in ST displacement could be attributed to changes in V_5 RWA, leaving 70% of this variability unexplained. ST elevation and depression owing to myocardial ischemia undoubtedly accounted for some of the remaining variability in ST segments.

There are reasons to believe that our data may be applicable to the majority of patients undergoing cardiac operations. First, RWA reduction with the Canadian retractor was evident regardless of whether patients had LVH. As anticipated, patients with LVH had larger V_5 RWAs at baseline and after retraction, yet the degree of shrinkage in RWA was similar in patients with and without LVH. Although ST depression during exercise testing in patients with LVH has a high false-positive rate (17), intraoperative ECG monitoring for myocardial ischemia is commonly performed in these patients, and more marked changes in ST segments are required before ischemia is diagnosed (2). Perhaps an RWA gain correction factor will prove even more important in these patients.

Another reason why our data may pertain to a wide variety of patients is suggested by the observation that V_5 RWA shrinkage is similar in patients undergoing both CABG and valvular operations. As our data included only 19 patients having non-CABG surgery, this result requires future confirmation.

To estimate the magnitude and importance of the V_5 RWA changes observed with the Canadian retractor, we examined RWA changes temporally associated with other intraoperative mechanical phenomena. The Favaloro retractor caused substantial changes in V_5 RWA in more than half the patients (Figure 2, upper panel), but there was no predictable shrinkage or amplification in RWA, unlike that noted with the Canadian retractor. During spontaneous ventilation, variation in V_5 RWA over the respiratory cycle was limited to a few patients; in contrast, variation in V_5 RWA during positive pressure ventilation occurred in more than one-third of the patients studied. However, these respiratory changes in RWA were not as marked as those noted with either retractor.

A surprising observation in this study was the marked V_5 RWA change after chest closure at end-operation. However, as only 68 of 83 patients had data available for analysis, it is premature to directly compare these end-operative changes with those occurring during surgical retraction. The presence of marked RWA changes at end-operation raises the question of when, if ever, these ECG changes fully resolve. This observation may complicate investigation of postoperative ischemia using ECG techniques, particularly when small changes in ST segments are followed continuously and summed over time (18).

Although the mechanism for the RWA changes was not elucidated by our study, the explanation may not be as simple as a physical deformation of the chest wall and movement of the V_5 lead relative to the heart. Were this the case, sternal closure may have restored RWAs to baseline levels. Factors that may influence RWA include cardiac volume (19), ventricular function (20,21), and the state of lung inflation (22). We propose that the use of sternal retractors be added to this list.

Several limitations of our study must be addressed. First, our study emphasized R-wave changes in V_5, rather than in other electrocardiographic leads. We chose this lead because it is the most sensitive lead (1,2) for detection of intraoperative myocardial ischemia, and we suspect it is the most common single lead chosen for ischemia monitoring. A second limitation of our study was the heterogeneous nature of the population studied. However, subgroup analyses showed that RWA reduction with the Canadian retractor occurred in patients with and without LVH and undergoing both CABG and valvular operations. Although preliminary, these results suggest that our findings may apply to the majority of patients undergoing cardiac operations through a median sternotomy. Lastly, we chose a subgroup of patients to examine the relation between V_5 RWAs and ST displacements. As the majority of patients had minor baseline ST abnormalities (≤0.4 mm elevation or depression) or isoelectric ST segments, inclusion of these patients in a regression analysis would have obscured any existing relation. For example, a patient with an isoelectric ST segment could not possibly show any shrinkage or amplification of the ST deviation regardless of any concomitant change in RWA. Similarly, patients with minor ST abnormalities that changed sign on retraction (ST depression of −0.1 mm changing to ST elevation of +0.1 mm) posed a problem—did these ST deviations shrink, magnify, or remain unchanged? Choosing a subgroup of patients with initial ST deviations of 0.5 mm or greater, and which did not change signs, obviated these problems. Although the relationship between RWA and ST displacement could be analyzed in only 37 patients, the statistical significance of our results suggests that this relation is unlikely the result of chance in this subpopulation.

In summary, changes in V_5 RWA are common during cardiac operations. Both Favaloro and Canadian sternal retractors alter V_5 RWA, but only the latter causes a predictable shrinkage in V_5 RWA. As changes in RWA account for a significant amount of the variability in ST-segment elevation or depression, improved perioperative ECG monitoring may result from inclusion of an RWA gain correction in ST-segment analysis. Such a gain correction could be incorporated into intraoperative computer-aided ST-segment monitoring algorithms.

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References

1. Roy WL, Edelist G, Gilbert B. Myocardial ischemia during noncardiac surgical procedures in patients with coronary-artery disease. Anesthesiology 1979;51:393–7.
2. London MJ, Hollenberg M, Wong MG, et al. Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. Anesthesiology 1988;69:232–41.
3. Kotrly KJ, Kotter GS, Mortara D, Kampine JP. Intraoperative detection of myocardial ischemia with an ST segment trend monitoring system. Anesth Analg 1984;63:343–5.
4. Leung JM, O'Kelly B, Browner WS, et al. Prognostic importance of postbypass regional-wall motion abnormalities in patients undergoing coronary artery bypass graft surgery. Anesthesiology 1989;71:16–25.
5. Smith JS, Cahalan MK, Benefiel DJ, et al. Intraoperative detection of myocardial ischemia in high-risk patients. Electrocardiography versus 2-dimensional transesophageal electrocardiography. Circulation 1985;72:1015–21.
6. Van Daele MERM, Sutherland GR, Mitchell MM, et al. Do changes in pulmonary capillary wedge pressure adequately reflect myocardial ischemia during anesthesia? A correlative preoperative hemodynamic, electrocardiographic, and transesophageal echocardiographic study. Circulation 1990;81:865–71.
7. Gerson MC, Morris SN, McHenry PL. Relation of exercise-induced physiologic ST-segment depression to R wave amplitude in normal subjects. Am J Cardiol 1980;46:778–82.
8. Hakki A-H, Iskandrian AS, Kutalek S, Hare TW, Sokoloff NM. R-wave amplitude: a new determinant of failure of patients with coronary heart disease to manifest ST segment depression during exercise. J Am Coll Cardiol 1984;3:1155–60.
9. Hollenberg M, Go M, Massie BM, Wisneski JA, Gertz EW. Influence of R-wave amplitude on exercise-induced ST depression: need for a "gain factor" correction when interpreting stress electrocardiograms. Am J Cardiol 1985;56:13–7.
10. Goldman MJ. Principles of clinical electrocardiography. Los Altos: Wang Medical Publications, 1979:8.
11. Goldman MJ. Principles of clinical electrocardiography. Los Altos: Wang Medical Publications, 1979:frontispiece.
12. Ellis JE, Roizen MF, Aronson S, Feinstein SB, Briller JE. Frequency with which ST segment trends predict intraoperative myocardial ischemia (abstract). Anesthesiology 1987;67:A2.
13. Hollenberg M, Zoltick JM, Go M, et al. Comparison of a quantitative treadmill exercise score with standard electrocardiographic criteria in screening asymptomatic young men for coronary artery disease. N Engl J Med 1985;313:600–6.
14. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.
15. Slogoff S, Keats AS. Further observations on perioperative myocardial ischemia. Anesthesiology 1986;65:539–42.
16. Leung JM, O'Kelly BF, Mangano BT, SPI Research Group. Relationship of regional wall motion abnormalities to hemodynamic indices of myocardial oxygen supply and demand of patients undergoing CABG surgery. Anesthesiology 1990;73:802–14.
17. Hammill SC, Khandheria BK. Silent myocardial ischemia. Mayo Clin Proc 1990;65:374–83.
18. Siliciano D, Hollenberg M, Goehner P, Mangano DT. Use of continuous vs. intermittent narcotic after CABG surgery. Effects on myocardial ischemia (abstract). Anesth Analg 1990;70:S371.
19. Brody DA. A theoretical analysis of intracavitary blood mass influence on the heart-lead relationship. Circ Res 1956;4:731–8.
20. Bonoris PE, Greenberg PS, Castellanet MJ, Ellestad MH. Significance of changes in R wave amplitude during treadmill stress testing: angiographic correlation. Am J Cardiol 1978;41:846–51.
21. Bonoris PE, Greenberg PS, Christison GW, Castellanet MJ, Ellestad MH. Evaluation of R wave amplitude changes versus ST-segment depression in stress testing. Circulation 1978;57:904–10.
22. Toyama J, Okada A, Nagata Y, Okajima M, Yamada K. Electrocardiographic changes in pulmonary emphysema: effects of experimentally induced overinflation of the lungs on QRS complexes. Am Heart J 1974;87:606–13.

Effect of α-Stat Versus pH-Stat Strategy on Oxyhemoglobin Dissociation and Whole-Body Oxygen Consumption During Hypothermic Cardiopulmonary Bypass

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To determine whether α-stat or pH-stat strategy should be used, 20 patients undergoing coronary artery bypass grafting during moderate hypothermic hemodilutional cardiopulmonary bypass were studied. The carbon dioxide management during bypass was randomly done according to α-stat strategy in 10 patients (i.e., temperature-uncorrected $Paco_2$ was kept near 40 mm Hg and uncorrected pHa was kept at about 7.4) and according to pH-stat strategy in the other 10 patients (i.e., temperature-corrected $Paco_2$ was kept near 40 mm Hg and uncorrected pHa was kept at about 7.4). In both groups, when the central venous temperature was stable at 26.5 ± 2.5°C, the perfusion flow was altered sequentially from 2.4 to 1.8 and 1.2 $L \cdot min^{-1} \cdot m^{-2}$. The mixed venous oxyhemoglobin saturation at the different perfusion flows was monitored by the Oxy-Stat meter and was correlated with the corresponding mixed venous oxygen tension to construct an oxyhemoglobin dissociation curve. Also, the whole-body oxygen consumption at the different perfusion flows was computed. The whole-body oxygen consumption and the oxyhemoglobin dissociation were not significantly different between the α-stat and the pH-stat groups. In both groups, the dissociation curve is shifted to the left, but the oxygen consumption per unit time does not significantly change despite decreasing the perfusion flow from 2.4 to 1.2 $L \cdot min^{-1} \cdot m^{-2}$. The results suggest that oxygen delivery is not impaired during moderate hypothermic cardiopulmonary bypass independent of whether α-stat or pH-stat strategy is used.

(Anesth Analg 1992;74:32–7)

The strategy of acid-base management during hypothermic cardiopulmonary bypass (CPB) has been a controversial issue (1–3). Two main strategies of acid-base management may be followed during hypothermic CPB: pH-stat, whereby a temperature-corrected $Paco_2$ of near 40 mm Hg and corrected pHa near 7.4 are maintained at the different body temperatures; and α-stat whereby the temperature-uncorrected $Paco_2$ (measured at 37°C) is kept near 40 mm Hg and the uncorrected pHa is kept near 7.4, irrespective of the body temperature (2,3).

Hypothermia shifts the oxyhemoglobin dissociation curve to the left (4). The leftward shift may be exaggerated by the relative alkalosis that characterizes the α-stat strategy of acid-base regulation (5). Thus, hypothermia and alkalosis may be a double hazard that reduces the available oxygen (6). In contrast with α-stat, the pH-stat strategy of acid-base regulation maintains the temperature-corrected pHa and $Paco_2$ during hypothermia at the normothermic values and hence may be used to counter the leftward shift of the oxyhemoglobin dissociation curve engendered by hypothermia (3).

The present report compares the effect of pH-stat versus α-stat management on the oxyhemoglobin dissociation in two groups of patients undergoing coronary artery bypass grafting during moderate hypothermic CPB. In the two groups, the perfusion flow was altered to achieve a spectrum of mixed venous oxyhemoglobin saturation ($S\bar{v}o_2$) and mixed venous oxygen tension ($P\bar{v}o_2$) values that can be correlated. Also, the whole-body oxygen consumption ($\dot{V}o_2$) values at the different perfusion flows were compared.

Methods

The investigation was performed on 20 patients, aged 40–75 yr and weighing 60–90 kg, who were undergoing coronary artery bypass grafting. The patients

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were randomized with respect to carbon dioxide management during CPB into two groups. In 10 patients, the temperature-uncorrected Paco$_2$ was maintained at about 40 mm Hg (α-stat), whereas the temperature-corrected Paco$_2$ was maintained at this range in the other 10 patients (pH-stat). The investigation was approved by the Institution Research Committee, and informed consent was obtained.

All patients were premedicated with 10 mg of morphine, 25 mg of promethazine, and 0.4 mg of scopolamine, intramuscularly. Anesthesia was induced with 0.1 mg/kg of midazolam, 50 μg/kg of fentanyl, and a mixture of 0.1 mg/kg of vecuronium and 0.1 mg/kg of pancuronium IV. After orotracheal intubation, ventilation was controlled with 100% oxygen, without any inhaled anesthetic supplementation. Patients were monitored with an electrocardiogram (V_5), a radial artery catheter, and a pulmonary artery catheter.

Before CPB, the patients were given lactated Ringer's solution at a rate of 10 mL/kg, and an additional 1500 mL was used to prime the Bentley bubble oxygenator (Bentley-10, American Bentley). No blood or colloid was added to the prime. During bypass, the mean hematocrit level was 23.9% ± 3.5% in the α-stat group and 24.1% ± 2.9% in the pH-stat group. The patients were perfused by a roller pump (Sarns 5000, Ann Arbor, Mich.) at a flow rate of 2.4 $L\cdot min^{-1}\cdot m^{-2}$, and the flow was monitored by a flow rate computer (Sarns). In the α-stat group of patients, an equal flow of 100% oxygen without any additional carbon dioxide was continuously delivered to the bubble oxygenator during hypothermia and after rewarming (7). In the pH-stat group, carbon dioxide was added to the oxygen flow delivered to the oxygenator and was adjusted according to blood gas results to maintain the temperature-corrected Paco$_2$ at around 40 mm Hg.

Continuous in-line oximetry of the venous saturation was achieved by the Oxy-Stat meter (8,9). The Oxy-Stat meter has shown accuracy and reliability during extracorporeal circulation, as evidenced by the excellent correlation between the oxyhemoglobin saturation measured by the Oxy-Stat meter and that determined by the van Slyke and Lex O_2 con (10). The site for body temperature and S$\bar{v}$o$_2$ monitoring, as well as mixed venous gas sampling, was the venous blood at the entrance to the pump oxygenator (11), whereas arterial blood was sampled simultaneously from the outlet of the oxygenator. Blood gas levels were measured by an ABL300 Radiometer with electrodes kept constant at 37°C. The temperature-uncorrected values measured at 37°C were then corrected automatically by the radiometer according to body temperature. In the ABL300 blood gas analyzer, correction is done by using formulas based on work by Severinghaus (12) for pH, by Siggard-Anderson (13) for Pco$_2$ and by Severinghaus et al. (14) for Po$_2$.

During CPB, body temperature was decreased, and the heart was arrested after aortic cross-clamping with a cardioplegic solution (K^+, 30 mEq/L at 4°C). After 10–20 min of CPB, a steady state of perfusion was achieved and the mean body temperature was stabilized at 26.5 ± 2.5°C. In both the α-stat and the pH-stat groups, the S$\bar{v}$o$_2$ as well as the mixed venous and arterial blood gases were monitored simultaneously when the perfusion flow was maintained at 2.4 $L\cdot min^{-1}\cdot m^{-2}$. The perfusion flow was then decreased in sequence to 1.8 and 1.2 $L\cdot min^{-1}\cdot m^{-2}$. The resulting S$\bar{v}o_2$ and blood gas values were recorded 5 min after each perfusion flow change. The S$\bar{v}$o$_2$ values achieved at the different perfusion flows were correlated with the corresponding temperature-corrected P$\bar{v}$o$_2$ values in the two groups of patients to construct oxyhemoglobin dissociation curves.

The $\dot{V}$o$_2$ values at the different perfusion flows were computed as the product of the arterial-venous oxygen content difference multiplied by the perfusion flow:

$$\dot{V}o_2\ (mL\cdot min^{-1}\cdot m^{-2}) = \{[(Sao_2\% - S\bar{v}o_2\%) \times Hb \times 1.36] + [(Pao_2 - P\bar{v}o_2) \times 0.003]\} \times CI,$$

where CI = perfusion flow index ($dL\cdot min^{-1}\cdot m^{-2}$); Sao$_2$% = arterial oxygen saturation, computed by the Radiometer; S$\bar{v}$o$_2$% = mixed venous oxygen saturation, measured by the Bentley oximeter; Hb = hemoglobin concentration (g/dL), calculated as hematocrit /3; 1.36 = Hüffner factor; Pao$_2$ = uncorrected arterial oxygen tension (mm Hg); P$\bar{v}$o$_2$ = uncorrected mixed venous oxygen tension (mm Hg); 0.003 = solubility coefficient of oxygen at 37°C.

All data are presented as mean ± SD. Analysis of variance was used to compare the mean values at the different perfusion flows.

Regression analysis was conducted between the different perfusion flows and P$\bar{v}$o$_2$, S$\bar{v}$o$_2$, and $\dot{V}$o$_2$ values in both the α-stat and pH-stat groups. Also, the S$\bar{v}$o$_2$ value was correlated with the corresponding P$\bar{v}$o$_2$ value to construct an oxyhemoglobin dissociation curve. As the oxyhemoglobin dissociation curve is sigmoid, correlation of P$\bar{v}$o$_2$ and S$\bar{v}$o$_2$ was conducted by correlating log P$\bar{v}$o$_2$ with the probit of S$\bar{v}$o$_2$. The log-probit transformation straightens the sigmoid curve (15) and facilitates the determination of P50 values. The *t*-test of significance was used to compare the slopes (*b*) and intercepts (*a*) of regression lines. Significant results were identified when the F ratio deviated significantly from 1, the null hypothesis of no difference. $P < 0.05$ was considered significant.

Table 1. Mean Temperature-Corrected and Uncorrected pHa and Paco_2 at the Different Perfusion Flows in the α-Stat Group and the pH-Stat Group

Flow index ($\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$)	α-Stat				pH-Stat			
	Paco_2 (mm Hg)		pHa		Paco_2		pHa	
	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected	Corrected
2.4	37.2 ± 4.6	24.6 ± 3.5	7.42 ± 0.05	7.55 ± 0.06	57.4 ± 4.7	36.5 ± 2.9	7.30 ± 0.03	7.40 ± 0.03
1.8	33.8 ± 3.6	22.4 ± 3.7	7.45 ± 0.05	7.58 ± 0.06	56.0 ± 4.0	35.2 ± 5.2	7.30 ± 0.02	7.40 ± 0.03
1.2	32.9 ± 3.3	21.9 ± 3.0	7.47 ± 0.04	7.59 ± 0.06	55.2 ± 3.3	35.4 ± 2.3	7.30 ± 0.03	7.40 ± 0.05

Decreasing of the perfusion flow index from 2.4 to 1.8 and 1.2 $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ did not result in a significant change of Paco_2 and pHa in both the α-stat and pH-stat groups ($P < 0.05$).

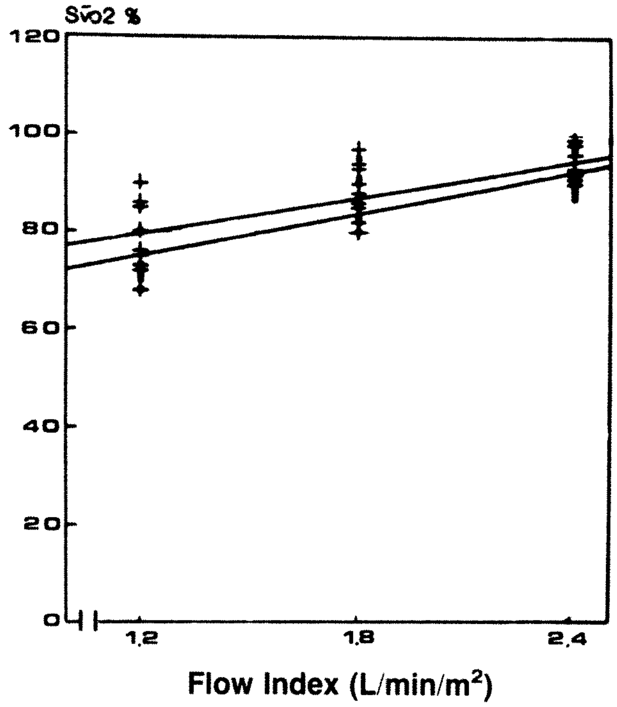

Figure 1. Results of correlation and regression showing a significant positive linear relationship between $\text{S}\bar{\text{v}}\text{o}_2$ and flow index in α-stat (●; $r = 0.829$, $b = 14.5$, $a = 57.6$, $P < 0.001$) and in pH-stat (+ ; $r = 0.759$, $b = 12.6$, $a = 64.4$, $P < 0.001$). No significant difference was noted in comparison of slopes (*b*) and of intercepts (*a*).

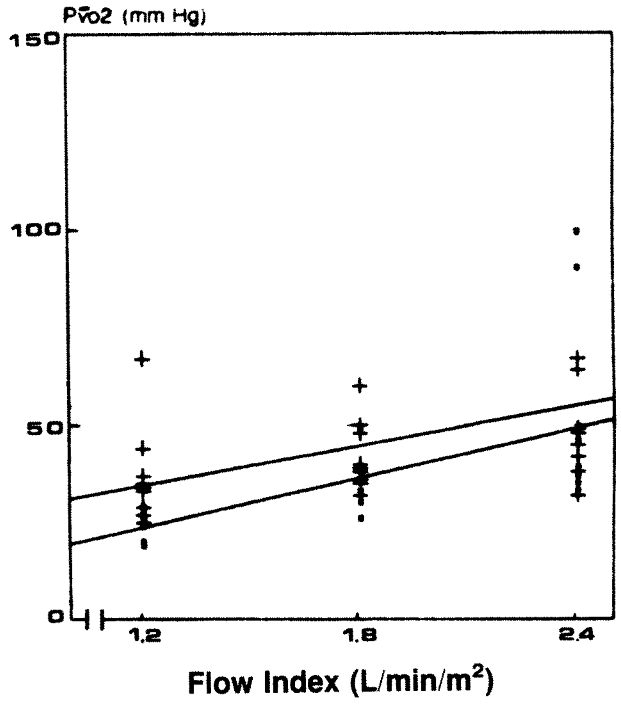

Figure 2. Results of correlation and regression showing a significant positive linear relationship between $\text{P}\bar{\text{v}}\text{o}_2$ and flow index in α-stat (●; $r = 0.603$, $b = 21.3$, $a = -1.68$, $P < 0.001$) and in pH-stat (+ ; $r = 0.460$, $b = 18.91$, $a = 11.05$, $P < 0.01$). No significant difference was noted in comparison of slopes (*b*) and of intercepts (*a*).

Results

In the α-stat groups, the mean value of the temperature-uncorrected pHa was 7.42 ± 0.05 and of the temperature-uncorrected Paco_2 37.2 ± 4.6 mm Hg. In the pH-stat group, the corrected pHa was 7.40 ± 0.03 and the corrected Paco_2 was 36.5 ± 2.9 mm Hg. In both groups, decreasing the perfusion flow from 2.4 to 1.8 and 1.2 $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ was not followed by any significant change in pHa or Paco_2 (Table 1).

In all patients, decreasing the perfusion flow was followed by a significant decrease of $\text{S}\bar{\text{v}}\text{o}_2$ (Figure 1) and $\text{P}\bar{\text{v}}\text{o}_2$ (Figure 2). The $\text{S}\bar{\text{v}}\text{o}_2$ and $\text{P}\bar{\text{v}}\text{o}_2$ changes were not significantly different whether α-stat or pH-stat strategy was used.

Correlation and regression of the probit of $\text{S}\bar{\text{v}}\text{o}_2$ on the log of the corresponding $\text{P}\bar{\text{v}}\text{o}_2$ did not significantly differ in the α-stat group from the pH-stat group (Figure 3). Estimation of the P50 from the regression lines showed a P50 of 11.9 mm Hg in the α-stat group, and a P50 of 12.1 mm Hg in the pH-stat group.

The $\dot{\text{V}}\text{o}_2$ value in both the α-stat and pH-stat groups was not significantly different when a perfusion flow of 2.4 $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ was used and did not

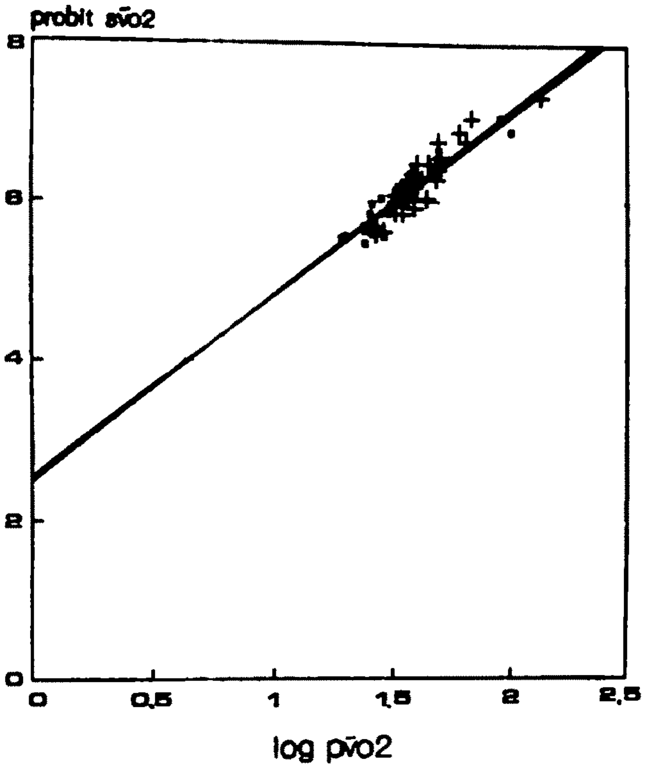

Figure 3. Results of correlation and regression of the probit of $S\bar{v}O_2$ on log $P\bar{v}O_2$ in α-stat (●; $r = 0.925$, $b = 2.33$, $a = 2.49$, $P < 0.001$) and in pH-stat (+ ; $r = 0.761$, $b = 2.28$, $a = 2.53$, $P < 0.001$). The two regression lines overlapped, and no significant difference was noted in comparison of slopes (*b*) and of intercepts (*a*).

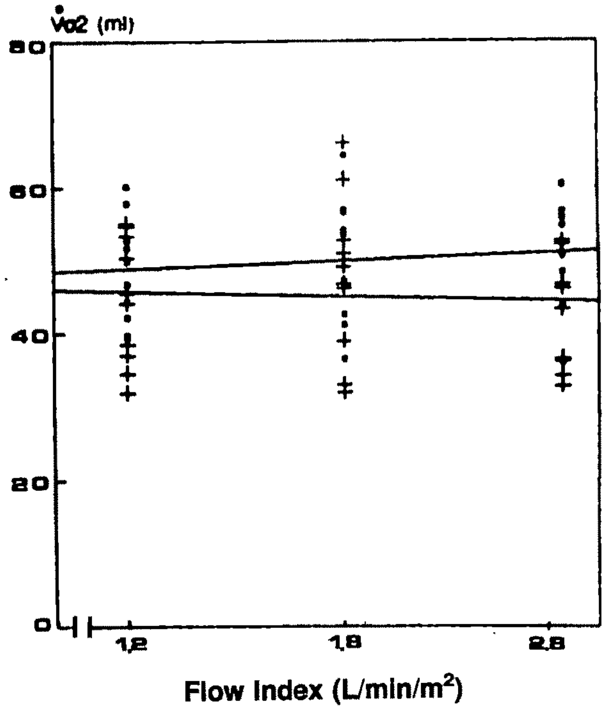

Figure 4. Results of correlation and regression showing a nonsignificant relationship between $\dot{V}O_2$ and flow index in α-stat (●; $r = 0.122$, $b = 1.85$, $a = 46.6$, $P = 0.519$) and in pH-stat (+ ; $r = -0.062$, $b = -1.14$, $a = 47.1$, $P = 0.745$). No significant difference was noted in comparison of slopes (*b*) and of intercepts (*a*).

show any significant change when the flow was decreased to 1.8 and 1.2 L·min^{-1}·m^{-2} (Figure 4).

The data from which the whole-body oxygen consumption was calculated are shown in Table 2.

Discussion

The acid-base management during hypothermic CPB has been controversial (1–3). Two approaches have been advocated. The α-stat strategy aims to maintain the temperature-uncorrected pHa near 7.4 and the uncorrected $PaCO_2$ near 40 mm Hg. The second strategy is the pH-stat, which maintains the temperature-corrected pHa and $PaCO_2$ near these levels (5). In our first group of patients, the mean temperature-uncorrected pHa was 7.42 ± 0.05 and the mean uncorrected $PaCO_2$ was 37.2 ± 4.6 mm Hg, which match the α-stat strategy. In the second group, the mean temperature-corrected pHa was 7.40 ± 0.03 and the mean corrected $PaCO_2$ was 36.5 ± 2.9 mm Hg, which match the pH-stat strategy. Changing the perfusion flow in both groups while keeping the oxygen flow constant does not result in any significant change of pHa or $PaCO_2$, suggesting that perfusion flow is not the predominant factor determining $PaCO_2$ during CPB.

In both the α-stat and the pH-stat groups, the perfusion flow during CPB is altered sequentially to construct an oxyhemoglobin dissociation curve by correlating the subsequent changes of $S\bar{v}O_2$ with the corresponding $P\bar{v}O_2$ values. In both groups, decreasing the perfusion flow from 2.4 to 1.8 and 1.2 L·min^{-1}·m^{-2} is followed by a significant decrease of $S\bar{v}O_2$ and $P\bar{v}O_2$, denoting increased hemoglobin desaturation when the perfusion flow is decreased (9). The $S\bar{v}O_2$ and $P\bar{v}O_2$ values at the different perfusion flows are not significantly different whether pH-stat or α-stat strategy is used. Also, correlation and regression of $S\bar{v}O_2$ values achieved at the different perfusion flows with the corresponding $P\bar{v}O_2$ values overlaps in the two groups, and shows a P50 of 11.9 mm Hg in the α-stat group and a P50 of 12.1 mm Hg in the pH-stat group (not significantly different). These values are significantly lower than the standard normothermic P50 value of 27 mm Hg, confirming the leftward shift of the oxyhemoglobin dissociation curve by hypothermia (4). However, the similar P50 value in both the α-stat and pH-stat groups is unexpected in view of the known effect of pH and PCO_2 on the oxyhemoglobin dissociation

Table 2. Data From Which the Whole-Body Oxygen Consumption Was Calculated at the Different Perfusion Flows in Both the α-Stat and pH-Stat Groups

Flow ($L \cdot min^{-1} \cdot m^{-2}$)	$P\bar{v}o_2$	$S\bar{v}o_2$	Pao_2	Sao_2	Hct
α-Stat					
2.4	85.0 ± 32.3	91.2 ± 3.7	474.4 ± 121.3	99.87 ± 0.09	23.9 ± 3.5
1.8	62.5 ± 13.1	86.2 ± 4.6	524.3 ± 133.6	99.39 ± 1.58	23.9 ± 3.5
1.2	44.9 ± 6.5	73.8 ± 5.8	450.5 ± 106.2	99.88 ± 0.04	23.9 ± 3.5
	$P = 0.0007$	$P < 0.00001$	NS	NS	NS
pH-Stat					
2.4	98.1 ± 32.4	94.1 ± 3.0	486.9 ± 89.3	99.87 ± 0.06	24.1 ± 2.9
1.8	69.8 ± 21.6	88.0 ± 5.5	520.9 ± 86.2	99.89 ± 0.03	24.1 ± 2.9
1.2	65.7 ± 17.5	79.0 ± 7.3	545.7 ± 81.3	99.9 ± 0.00	24.1 ± 2.9
	$P = 0.0129$	$P < 0.00001$	NS	NS	NS

$P\bar{v}o_2$, temperature-uncorrected venous oxygen tension; $S\bar{v}o_2$, mixed venous oxyhemoglobin saturation; Pao_2, temperature-uncorrected arterial oxygen tension; Sao_2, arterial oxyhemoglobin saturation; Hct, hematocrit percentage.

The Pao_2 and Sao_2 values did not significantly change (NS) with changing perfusion flow, whereas $P\bar{v}o_2$ and $S\bar{v}o_2$ decreased significantly with decreasing flow ($P < 0.05$).

curve (4). If blood is cooled in a sealed environment (16), the oxyhemoglobin dissociation curve is shifted to the left secondary to lowering of temperature by about 5.7% per °C, while the increase in affinity of hemoglobin for oxygen owing to the rise in pH is only 1.7% per °C. It is possible that during hypothermia, the effect of cooling on the oxyhemoglobin dissociation overshadows the effect of pH and Pco_2 within the range difference between the pH-stat and the α-stat groups. Also, Bickler (17) recently found in lizards that the intracellular pH of brain stayed constant over an 18–35°C temperature range (i.e., pH-stat), whereas other tissue compartments including blood conformed to the α-stat model. These data point out that intracellular acid-base regulation can be independent of blood regulation and does not always follow α-stat (1). This may apply to the intracellular pH of red blood corpuscles and may minimize the effect of pH-stat versus α-stat on oxyhemoglobin dissociation during hypothermia.

Despite the leftward shift of the oxyhemoglobin dissociation curve by hypothermia, the whole-body oxygen consumption does not significantly change when the perfusion flow is decreased as low as $1.2\ L \cdot min^{-1} \cdot m^{-2}$, whether pH-stat or α-stat strategy is used. This may be attributed to the decrease of whole-body oxygen consumption during hypothermia by about 50% for every 10°C decrease in body temperature (18,19). Also, the degree of leftward shift of the oxyhemoglobin dissociation curve by hypothermia is about 7.4% per °C, which is approximately equal to the decrease of Po_2 secondary to its increased oxygen solubility (20). The increased solubility of oxygen in plasma by cooling is associated with a concomitant increased affinity of hemoglobin and tissues for oxygen to the same degree, and hence the oxygen diffusion gradient and oxygen delivery may not be impaired (17).

During normothermia, oxygen consumption at stable conditions is equal to oxygen demand. When the oxygen supply (product of cardiac output and arterial oxygen content) decreases to below a critical value, oxygen extraction becomes less efficient, so that the oxygen consumption starts to decrease and becomes supply-dependent (21). The critical level of oxygen supply during normothermia is about 8–10 $mL \cdot kg^{-1} \cdot min^{-1}$ (22). This may not apply to hypothermia. In our patients during hemodilutional hypothermic CPB, the oxygen consumption is not decreased despite decreasing the perfusion flow to $1.2\ L \cdot min^{-1} \cdot m^{-2}$. The oxygen supply under these conditions is approximately 2–3 $mL \cdot kg^{-1} \cdot min^{-1}$. Thus, hypothermia does not impair oxygen delivery whether α-stat or pH-stat is used and may even increase the safety margin and decrease the critical oxygen supply necessary to maintain the required oxygen demand.

In conclusion, oxyhemoglobin dissociation and whole-body oxygen consumption are not significantly different between the α-stat and the pH-stat groups during hypothermic CPB. In both groups, the dissociation curve is shifted to the left, but the $\dot{V}o_2$ does not significantly change despite decreasing the perfusion flow to as low as $1.2\ L \cdot min^{-1} \cdot m^{-2}$. The results suggest that oxygen delivery is not impaired during moderate hypothermic CPB whether pH-stat or α-stat strategy is used.

References

1. Hickey PR, Hansen DD. Temperature and blood gases: the clinical dilemma of acid-base management for hypothermic

cardiopulmonary bypass. In: Tinker JH, ed. Cardiopulmonary bypass: current concepts and controversies. Philadelphia: WB Saunders, 1989:1–20.

2. Tinker JH, Campos JH. Pro: blood gases should be corrected for temperature during cardiopulmonary bypass: pH-stat mode. Cardiothorac Anesth 1988;2:701–4.
3. Murkin JM. Con: blood gases should not be corrected for temperature during hypothermic cardiopulmonary bypass: α-stat mode. J Cardiothorac Anesth 1988;2:705–7.
4. Severinghaus JW. Oxyhemoglobin dissociation curve correction for temperature and pH variation in human blood. J Appl Physiol 1958;12:485.
5. White FN, Weinstein Y. Carbon dioxide transport and acid-base balance during hypothermia. In: Utley JR, ed. Pathophysiology and techniques of cardiopulmonary bypass. Volume 2. Baltimore: Williams & Wilkins, 1983:40–8.
6. Finlayson DC, Kaplan JA. Cardiopulmonary bypass. In: Kaplan JA, ed. Cardiac anesthesia. Orlando, Fla.: Grune & Stratton, 1979:405.
7. Baraka A, Haroun S, Baroody M, Dabbous A, Siddik S, Sibai A. Effect of oxygen flow on P_{CO_2} and P_{O_2} during cardiopulmonary bypass. J Extra-Corporeal Tech 1990;22:35–9.
8. Page PA, Birenbaum IB, Thomas L, et al. Optimizing cardiopulmonary bypass utilizing continuous oxygen saturation monitoring. J Extra-Corporeal Tech 1984;16:62–7.
9. Baraka A, Baroody M, Haroun S, et al. Continuous venous oximetry during cardiopulmonary bypass: influence of temperature changes, perfusion flow, and hematocrit levels. J Cardiothorac Anesth 1990;4:35–8.
10. Iatridids A, Heinemann S, De Rocher R, Osborn J. Continuous monitoring of blood oxygen saturation during extracorporeal circulation. J Extra-Corporeal Tech 1981;13:233–6.
11. Swan A. Metabolic rate, temperature, and acid-base control: the best strategy and our needs to achieve it. J Extra-Corporeal Tech 1985;17:65–73.
12. Severinghaus JW. Blood gas calculation. J App Physiol 1966; 21:1108–16.
13. Siggard-Anderson O. The acid-base status of the blood. 4th ed. Copenhagen: Munksgaard, 1974.
14. Severinghaus JW, Stafford M, Thumstrom AM. Estimation of skin metabolism and blood flow with tc P_{O_2} and tc P_{CO_2} electrodes by cuff occlusion of the circulation. Acta Anaesthesiol Scand Suppl 1978;68:9–15.
15. Tallerida RJ, Jacob LS. Construction of dose-response curves: statistical considerations. In: Tallerida RJ, Jacob LS, eds. The dose-response relation in pharmacology. New York: Springer Verlag, 1979:85.
16. Rupp SM, Severinghaus JW. Hypothermia. In: Miller RD, ed. Anesthesia. 2nd ed. Volume 3. New York: Churchill-Livingstone, 1986:1995–2022.
17. Bickler PE. Intracellular pH in the lizard *Dipsosaurus* in relation to changing body temperature. J Physiol (Lond) 1982;53:1466–72.
18. Harris EA, Seelye ER, Squire AW. Oxygen consumption during cardiopulmonary bypass with moderate hypothermia in man. Br J Anaesth 1971;43:113–20.
19. Hickey RF, Hoar PF. Whole-body oxygen consumption during low-flow hypothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg 1983;86:903–6.
20. Longmuir IS. The effect of hypothermia on the affinity of tissues for oxygen. Life Sci 1962;1:297–300.
21. Vincent JL. The relationship between oxygen demand, oxygen uptake, and oxygen supply. Intensive Care Med 1990;16(Suppl 2):S145–8.
22. Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. Am J Physiol 1965;209: 604–8.

Comparison of Thromboxane Synthetase Inhibitor and Methylprednisolone Effects on Protamine Responses in Dogs

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Neutralization of heparin anticoagulation by protamine produces catastrophic hemodynamic reactions in some patients. Using a canine model, we tested effects of thromboxane synthetase inhibition (CGS-13080) and glucocorticoid pretreatment on the cardiorespiratory effects of protamine. In control dogs, protamine decreased mean arterial pressure and cardiac output and increased mean pulmonary artery pressure, systemic and pulmonary vascular resistances (SVR, PVR), and airway pressure. Both CGS-13080 and methylprednisolone ameliorated some effects of protamine. CGS-13080 infusion decreased mean pulmonary artery pressure, SVR, and airway pressure after protamine injection relative to controls. Cardiac output and PVR were unaffected by the drug, whereas the decrease in mean arterial pressure was prolonged. Plasma thromboxane A_2 metabolite (TXB_2) concentrations were lower and prostacyclin metabolite (6-keto $PGF_{1\alpha}$) concentrations were higher compared with that of controls. These experiments support a role for TXA_2 in the response to protamine. Methylprednisolone pretreatment produced larger cardiac output and lower airway pressure after protamine injection compared with controls. Mean arterial pressure was improved, but not significantly. Mean pulmonary artery pressure, SVR, and PVR were not different from that of controls; TXB_2 and 6-keto $PGF_{1\alpha}$ were unaffected. The effects of methylprednisolone appear unrelated to arachidonic acid metabolism, as TXB_2 and 6-keto $PGF_{1\alpha}$ levels were unaffected.

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The administration of protamine can cause severe pulmonary hypertension, bronchoconstriction, and systemic hypotension (1). Apart from the relatively rare anaphylactic immunoglobulin E- and G-mediated reactions to protamine (2), a nonimmunologic pathway through complement activation and eicosanoid generation, particularly thromboxane (TXA_2), may be responsible for many of the acute reactions observed during protamine reversal of heparin (3–5).

Studies of this reaction in animals have suggested the importance of TXA_2 in causing the hemodynamic responses, especially the pulmonary hemodynamic effects of protamine. Increased plasma concentrations of cyclooxygenase products after protamine reversal have been observed in sheep and pigs; metabolites of both TXA_2 and prostacyclin (PGI_2) are significantly increased (4,6). More important, the hemodynamic alterations associated with the reaction are effectively prevented with the cyclooxygenase inhibitor indomethacin (6). A role for TXA_2 has been suggested by the demonstration that a thromboxane synthetase inhibitor (7) and a thromboxane receptor antagonist (8) attenuate the deleterious response to protamine.

The purpose of this study was to further investigate the role of TXA_2 in the hemodynamic responses to protamine neutralization of heparin and to compare the effects of thromboxane synthetase inhibition with those of glucocorticoid pretreatment. We chose a dog model for these experiments based on our preliminary experiments in which we observed reproducible, profound systemic and pulmonary responses to protamine. Furthermore, several studies have demonstrated that dogs, compared with some other animals, are more sensitive to protamine reactions (1); this increased protamine sensitivity in dogs may be of allergic origin. The steroid in this study

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was therefore used as a drug with potentially protective actions against allergic, anaphylactoid reactions through several mechanisms, including inhibition of histamine release, complement activation, and arachidonic acid metabolism (9,10).

Methods

This study was approved in advance by the institutional Animal Care and Use Committee. Mongrel dogs weighing 20–25 kg were conditioned for 1 wk before the experiments. Dogs were used for three manipulations each, performed 1 wk apart. They were randomly assigned to the following groups, so that each of six dogs was included in each treatment group once: the control group, the methylprednisolone-pretreatment group, and the thromboxane synthetase inhibitor-treatment group. All dogs were anesthetized with 20 mg/kg of thiopental, tracheally intubated, and ventilation-controlled during the experiments. Anesthesia was maintained with 1.5% halothane in oxygen. The dogs were intravenously paralyzed with 0.08 mg/kg of pancuronium. After each experiment, the dogs were closely monitored until they recovered from anesthesia. They were then allowed to recover for 1 wk until the next experiment.

Experiments were performed under sterile conditions. Polyethylene catheters were inserted into the femoral artery to measure mean arterial pressure (MAP), sample blood, and infuse drugs. Flow-directed pulmonary artery catheters were advanced into the pulmonary artery from the femoral vein and served for determination of mean pulmonary artery pressure (MPAP), mean pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) (thermal dilution method; mean of at least two measurements). Airway pressures were recorded through the endotracheal tube.

The control group intravenously received 300 IU/kg of heparin for anticoagulation, and 3 mg/kg of protamine sulfate was injected into the cephalic vein 10 min after heparin administration. The steroid-pretreated group was given 20 mg/kg of methylprednisolone (Solumedrol) (Upjohn, Kalamazoo, Mich.) intravenously 12 h and 2 h before heparin administration. The thromboxane synthetase inhibitor group was infused continuously with 0.3 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ of CGS-13080 (imidazo [1,5-a] pyridine-5-hexanoic acid) (CIBA-GEIGY Corp., Summit, N.J.) intraarterially. The infusion was started 15 min before heparin administration and was continued throughout the experiment.

Pressures were recorded on a four-channel recorder. Hemodynamic variables and airway pressures were measured before and after heparin injection and at 2, 5, 10, and 30 min after protamine injection. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated by the following standard formulas:

$$\text{SVR} = (\text{MAP} - \text{CVP})\cdot\text{CO}^{-1}\cdot 79.98\ (\text{dynes}\cdot\text{s}\cdot\text{cm}^{-5}),$$

$$\text{PVR} = (\text{MPAP} - \text{PCWP})\cdot\text{CO}^{-1}\cdot 79.98\ (\text{dynes}\cdot\text{s}\cdot\text{cm}^{-5}),$$

where CVP is central venous pressure.

Blood samples were obtained before heparin injection, before protamine injection, and 5 min after protamine injection. For measurement of TXB_2 (a stable metabolite of TXA_2) and 6-keto $\text{PGF}_{1\alpha}$ (a stable product of PGI_2), 5 mL of blood was collected from the indwelling femoral arterial line, letting blood flow freely into a precooled plastic tube containing 0.33 mL of sodium ethylenediamine tetraacetic acid (77 mM) and 0.167 mL of 1 mg/mL indomethacin solution. The blood was then centrifuged at 4°C. Plasma was decanted into a plastic tube and stored at −70°C until analysis.

Measurements of plasma TXB_2 and 6-keto $\text{PGF}_{1\alpha}$ were performed by radioimmunoassay. Standard eicosanoids were obtained from the Upjohn Company (Kalamazoo, Mich.); and stock solutions of 1 mg/mL in 10% vol/vol acetonitrile in water were prepared, diluted to 100 ng/mL, and stored at 4°C. Dilutions of standard compounds ranging from 0.074 to 18 ng/mL or of unknown samples were made in 0.05 M Tris-HCl (pH 6.8) containing 0.9% NaCl, 0.3% bovine serum albumin, 0.05% NaN_3, and 0.01 M ethylenediamine tetraacetic acid. ^{125}I-Methyl esters of TXB_2 and 6-keto-$\text{PGF}_{1\alpha}$, 2200 Ci/mmol, were obtained from Advanced Magnetics, Inc. (Cambridge, Mass.), as were rabbit antisera to TXB_2 and 6-keto-PGF_{1a}. Samples were assayed in duplicate. Standards or samples were mixed with ^{125}I-tracer, and the appropriate rabbit antiserum (all reagents at predetermined optimal levels) was added. The mixture was incubated for 16 h at 4°C in 25 × 75-mm polystyrene tubes. An excess of goat antirabbit antibody bound to paramagnetic particles was then added. The magnetic complexes were separated using a magnetic rack (Ciba-Corning Diagnostics, Walpole, Mass.), and the complexes were washed once. The bound radioactivity was determined using a gamma counter, and the samples were assessed against a standard curve.

All results are expressed as mean ± SE. A one-way analysis of variance was used to determine statistical differences between groups, followed by Dunnett's *t*-test for significance of individual comparisons. Statistical significance was assumed at $P < 0.05$.

Table 1. Effects of Protamine in Dogs Treated With Thromboxane Synthetase Inhibitor (CGS-13080) or Methylprednisolone

	Baseline	0.5 Min	2 Min	5 Min	10 Min	30 Min
Cardiac output (L/min)						
Control	4.3 ± 0.9	NA	1.6 ± 0.1^a	2.5 ± 0.5^a	3.5 ± 0.9	4.4 ± 0.8
CGS-13080	4.8 ± 0.6	NA	2.1 ± 0.5^a	1.8 ± 0.4^a	2.5 ± 0.3^a	4.2 ± 0.7
MP	5.8 ± 1.1	NA	4.4 ± 0.7^{a,b}	4.9 ± 0.8^c	5.0 ± 0.9	5.5 ± 0.9
Heart rate (beats/min)						
Control	142 ± 11	NA	123 ± 8^d	120 ± 7	124 ± 7	130 ± 11
CGS-13080	151 ± 19	NA	119 ± 10^a	121 ± 9^a	119 ± 9^a	128 ± 13^a
MP	128 ± 13	NA	118 ± 8	121 ± 8	125 ± 7	123 ± 6
Stroke volume (mL)						
Control	30.0 ± 4.3	NA	13.1 ± 1.6^a	21.2 ± 4.1	27.4 ± 5.5	32.8 ± 3.5
CGS-13080	32.2 ± 2.5	NA	19.1 ± 5.0^a	16.0 ± 4.1^a	22.1 ± 3.7^a	31.7 ± 2.5
MP	44.1 ± 4.2^c	NA	37.2 ± 5.0^{a,b}	40.8 ± 6.0^c	39.1 ± 4.6	43.8 ± 4.9
Mean arterial pressure (mm Hg)						
Control	127 ± 9	66 ± 12^a	87 ± 20^a	72 ± 17^a	106 ± 11	118 ± 8
CGS-13080	114 ± 10	39 ± 24^a	50 ± 14^a	48 ± 14^a	67 ± 12^{a,c}	86 ± 10^{c,d}
MP	118 ± 8	62 ± 6^a	130 ± 2	106 ± 6	108 ± 4	113 ± 5
Central venous pressure (mm Hg)						
Control	9.5 ± 0.9	NA	8.9 ± 1.0	9.5 ± 1.1	9.9 ± 0.9	9.9 ± 0.8
CGS-13080	9.1 ± 0.5	NA	9.1 ± 0.8	9.5 ± 0.9	9.1 ± 0.9	9.5 ± 0.9
MP	14.7 ± 2.9	NA	16.5 ± 3.4^c	15.2 ± 3.9	15.4 ± 3.8	16.3 ± 4.9
Systemic vascular resistance (dynes·s·cm^{-5})						
Control	2495 ± 340	NA	3996 ± 943^d	2232 ± 547	2596 ± 421	2236 ± 293
CGS-13080	1975 ± 338	NA	1646 ± 614^c	1616 ± 431	1839 ± 272	1731 ± 291
MP	1608 ± 184	NA	2353 ± 311^a	1708 ± 221	1735 ± 251	1613 ± 232
Mean pulmonary artery pressure (mm Hg)						
Control	22.5 ± 1.3	NA	33.3 ± 4.5^a	21.0 ± 1.9	21.2 ± 1.2	22.3 ± 1.3
CGS-13080	20.8 ± 1.3	NA	19.2 ± 2.0	14.5 ± 0.8^a	15.9 ± 0.5^d	18.5 ± 0.9
MP	21.3 ± 1.8	NA	35.5 ± 3.4^{a,c}	23.3 ± 1.3	20.7 ± 1.6	20.8 ± 2.0
Wedge pressure (mm Hg)						
Control	15.1 ± 1.6	NA	23.3 ± 4.2^a	13.5 ± 1.2	13.5 ± 1.2	14.7 ± 1.6
CGS-13080	12.8 ± 1.1	NA	9.3 ± 0.9^{a,b}	8.7 ± 1.0^{a,b}	9.2 ± 0.5^{a,c}	11.0 ± 1.2
MP	14.5 ± 2.2	NA	19.5 ± 2.5	12.5 ± 0.9	12.6 ± 1.6	13.8 ± 1.9
Pulmonary vascular resistance (dynes·s·cm^{-5})						
Control	147 ± 27	NA	532 ± 80^a	223 ± 50	202 ± 47	168 ± 41
CGS-13080	142 ± 20	NA	457 ± 125^a	315 ± 79	223 ± 25	154 ± 24
MP	105 ± 16	NA	327 ± 78^a	219 ± 35	155 ± 34	105 ± 17
Peak airway pressure (cm H_2O)						
Control	13.9 ± 1.5	NA	31.2 ± 4.9^a	20.2 ± 0.6	18.0 ± 0.8	14.7 ± 1.4
CGS-13080	15.0 ± 1.2	NA	18.4 ± 1.8^{a,c}	16.9 ± 1.4	15.6 ± 1.4	14.5 ± 1.4
MP	12.8 ± 1.6	NA	21.4 ± 2.4^a	15.4 ± 1.7^c	13.9 ± 1.2^c	13.2 ± 1.8

MP, methylprednisolone; NA, not available.
Values are mean ± SEM (of six measurements). Baseline values were measured after heparin but before protamine challenge.
$^aP < 0.01$ compared with baseline value.
$^bP < 0.01$ compared with the control group.
$^cP < 0.05$ compared with the control group.
$^dP < 0.05$ compared with baseline value.

Results

Pulmonary Hemodynamics and Airway Pressures

Protamine reversal in the control group caused significant increases in MPAP, PCWP, and PVR at 2 min (Table 1). These changes were accompanied by an increase in peak airway pressure. Airway pressure returned to normal slowly but was only significantly different from baseline value at 2 min.

Pretreatment with glucocorticoid did not prevent the increases in MPAP and PVR (Table 1). The increase in PCWP was less and not significantly different from baseline value (PCWP increased 25% in the methylprednisolone group and 54% in the control group); however, this attenuation did not result in a significant difference between the methylprednisolone and control groups. There was a less marked but significant increase in airway pressure in the methyl-

Table 2. Half-Recovery Time[a] After Protamine Reversal of Heparin Anticoagulation in Control Dogs and Dogs Treated With CGS-13080 or Methylprednisolone

Treatment group	Half-recovery time (min)
Control	3.47 ± 1.23
CGS-13080	11.18 ± 2.92[b]
Methylprednisolone	0.72 ± 0.17

Values are mean ± SEM of six observations.

[a] Time required for 50% recovery from decrease in mean arterial pressure.

[b] $P < 0.05$ compared with control group.

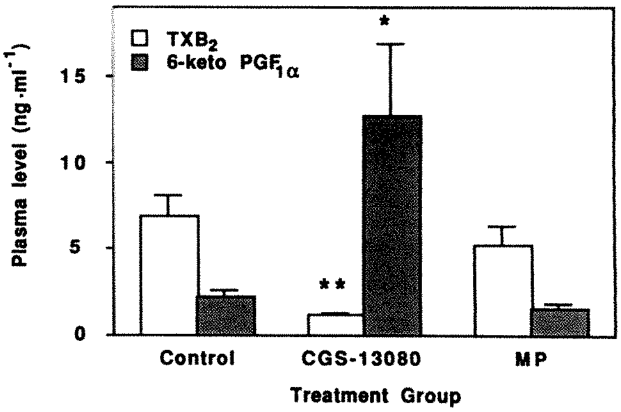

Figure 1. Plasma thromboxane B_2 (TXB_2; *open bars*) and 6-keto prostaglandin $PGF_{1\alpha}$ (6-keto $PGF_{1\alpha}$; *shaded bars*) in dogs 5 min after neutralization of heparin anticoagulation by protamine injection. The three groups were control, thromboxane synthetase inhibitor (CGS-13080)-treated, and methylprednisolone (MP)-treated dogs. Each *bar* represents the mean of six observations, with standard error illustrated by the vertical lines. $^*P < 0.05$; $^{**}P < 0.01$ compared with the control group.

prednisolone group at 2 min (41% in the methylprednisolone group and 58% in the control group), but this increase was transient and significantly reduced at 5 and 10 min compared with that of the control group.

CGS-13080 prevented completely the increase in MPAP and PCWP (Table 1). Compared with baseline values, MPAP in this group was significantly less at 5 and 10 min, and PCWP was significantly less at 2, 5, and 10 min. These values were also significantly different from that of the control group at 2, 5, and 10 min. However, PVR was significantly increased at 2 min and not different from control values. There was a small but significant increase in airway pressure at 2 min; this increase was significantly attenuated compared with that of controls.

Systemic Hemodynamics

In the control dogs, protamine administration caused significant decreases in CO, stroke volume (SV), MAP, and HR, and a significant increase in SVR (Table 1). Central venous pressure was unchanged.

In the methylprednisolone group, protamine caused small, significant reductions in CO and SV. These variables were significantly higher in these dogs than in controls at 2 and 5 min. In the methylprednisolone-pretreatment group, protamine caused a very transient but significant decrease in MAP 30 s after protamine administration. Although the MAP changes in this group were only transient, they were not significantly different from that of the control group, which displayed substantial variability at specific time points during recovery between dogs. Half-recovery time for the MAP changes was not significantly different from the control value (Table 2). Central venous pressure was significantly higher at 2 min compared with that of controls, but not different from baseline values (Table 1). Systemic vascular resistance increased significantly at 2 min compared with that at baseline and was not different from controls.

In the CGS-13080-treatment group, severe and significant decreases in CO, SV, and MAP occurred after protamine challenge (Table 1). Cardiac output and SV were not different from control values, whereas MAP was significantly less compared with that of controls at 10 and 30 min. CGS-13080 treatment significantly prevented the increase in SVR observed in controls.

Plasma Eicosanoids

Plasma TXB_2 and 6-keto $PGF_{1\alpha}$ increased dramatically during protamine reversal in the control group (preprotamine concentrations were not significantly different in the groups; only postprotamine levels are illustrated in Figure 1). The TXB_2 increased 10-fold after protamine injection compared with baseline values, whereas 6-keto $PGF_{1\alpha}$ increased threefold. Plasma eicosanoid concentrations 5 min after protamine injection are illustrated in Figure 1. Methylprednisolone-pretreatment had no effect on plasma levels. CGS-13080, on the other hand, resulted in a significant reduction in TXB_2 levels compared with the control group, coinciding with a significant increase in 6-keto $PGF_{1\alpha}$ levels.

Discussion

The results of our studies demonstrate that pretreatment of dogs with either the thromboxane synthetase inhibitor CGS-13080 or methylprednisolone attenuates some of the deleterious cardiorespiratory effects of protamine neutralization of heparin anticoagulation. However, the effects of the two drugs were markedly different, suggesting differences in their mechanisms of action in this experimental model. Furthermore, although our results do not clearly define how protamine produces cardiovascular deterioration in dogs, they suggest some differences between dogs and other species.

Pulmonary vasoconstriction owing to thromboxane release has been suggested as the primary pathogenic event in the cardiovascular deterioration caused by protamine in sheep and pigs (6–8). In our dogs, thromboxane-induced pulmonary vasoconstriction cannot completely account for the decreased CO and systemic hypotension because PVR was increased after protamine challenge in both the control and CGS-13080-treatment groups. The decreased CO after protamine challenge could be attributed to direct negative inotropic effects in the control group because PCWP was increased. In dogs pretreated with the thromboxane synthetase inhibitor, protamine injection was also followed by a decrease in CO, but this was accompanied by a marked decrease in cardiac filling pressure, suggesting reduced venous return in the CGS-13080 group. This observation, in conjunction with the reduced SVR, suggests systemic vasodilation in the CGS-13080-treated dogs. The increased prostacyclin observed after protamine challenge in the group pretreated with thromboxane synthetase inhibitor might account for this systemic vasodilation.

Pretreatment with methylprednisolone attenuated the bronchoconstriction and the severe drop in CO. However, methylprednisolone had no effect on the pulmonary hemodynamic events after protamine reversal or on the release of arachidonic acid metabolites. Despite the well-documented inhibitory effects of glucocorticoids on arachidonate metabolism in vitro (9), inhibitory effects of systemic steroid administration on plasma levels of products during pathophysiologic responses have not been consistently observed.

Heparin-protamine complexes are known to activate the complement system both through the classical and the alternative pathways (5,11), but the mechanisms involved are unclear. In patients reacting with bronchoconstriction, pulmonary hypertension, and systemic hypotension after protamine reversal, complement activation with release of the anaphylatoxins C3a and C5a has been demonstrated (4). It has been suggested that TXA_2 is generated through these anaphylatoxins, which alone also have potent vasoactive properties. They increase vascular permeability, cause histamine release from mast cells, constrict smooth muscle, and may well account for the anaphylactoid reactions experienced by some patients. Although corticosteroids have been documented to prevent complement activation, this treatment was not able to prevent all the deleterious effects of protamine reversal and had no effect on the release of thromboxane in the present study, indicating the complexity of mechanisms involved.

The role of histamine in this syndrome is controversial; in some studies it has been shown to be released (12), but not in others (13). Moreover, administration of histamine receptor blockers prevents the hemodynamic effects after protamine injection (14). In our study, it is not clear whether the beneficial effect of methylprednisolone treatment on bronchoconstriction and CO was caused by inhibition of histamine release.

The substantial improvement in CO in the steroid-treated group was accompanied by elevated CVP, with no significant improvement of other hemodynamic effects of protamine. These findings are suggestive of two possible mechanisms: steroid pretreatment might act by increasing blood volume owing to sodium retention or by enhancing cardiac inotropic activity. Although CVP was significantly increased in this group compared with control values on a statistical basis only after protamine challenge, basal CVP was in fact higher in this group (15 ± 3 vs 10 ± 1 mm Hg), supporting the former possibility. Against this argument, body weights of the dogs were unchanged (data not shown) during assignment to the three treatment groups (steroid, CGS-13080, and control). In favor of the second possibility, corticosteroids increase the density of β-adrenoceptors (15), which could account for both the increase in CO and the lower airway pressure in this group after protamine challenge. β-Adrenoceptor density was not measured in the present study. In fact, both mechanisms might contribute to the observed improvements.

Treatment of dogs with CGS-13080, the thromboxane synthetase inhibitor, altered several aspects of the response to protamine. Inhibition of thromboxane synthesis was confirmed by measurements of circulating levels of its major metabolite TXB_2, and as others have reported (6–8,16), this inhibition was associated with shunting of arachidonic acid metabolism toward prostacyclin production, evidenced by the rise in its metabolite, 6-keto $PGF_{1\alpha}$.

The shift to overproduction of the vasodilator PGI_2 instead of the vasoconstrictor TXA_2 in this group might be responsible for the severe aggravation and prolongation of systemic hypotension owing to a significant decrease in SVR. This in turn reduces afterload; but preload, evidenced by a significant drop in PCWP, was greatly reduced and may most likely account for the severe reduction in CO. Pulmonary artery pressure was also lower in this group, but this effect appears to be secondary to the other hemodynamic changes and not only due to inhibition of pulmonary vasoconstriction by TXA_2 because PVR was not significantly affected by the treatment. This is in accordance with what others have shown with thromboxane synthetase inhibitors (7). The circulatory derangements and the persistently increased PVR in this group appear to be a result of redirection of arachidonate toward other eicosanoid products.

Although our results suggest that thromboxane is a mediator of the reaction to protamine, other factors are involved as well; these might include histamine, serotonin, bradykinin, leukotrienes, and platelet activating factor, for example.

Some limitations of the present study should also be discussed. Although we calculated PVR using PCWP, a more accurate method is to calculate PVR on the basis of left atrial pressure. Eicosanoids were measured only before and 5 min after protamine challenge in this study. A more thorough approach in future experiments would be to sample blood more frequently to correlate changes in eicosanoid concentrations with hemodynamic changes. Further studies should also be performed with thromboxane receptor antagonists in this model to allow comparison to the present work with the thromboxane synthetase inhibitor.

In conclusion, this study demonstrates in the dog model the involvement of TXA_2 in the severe response to protamine reversal of heparin anticoagulation. Pretreatment with methylprednisolone had no apparent effects on eicosanoid production, but it was able to blunt the elevation in airway pressure and the reduction in CO. These effects might be attributed to enhancement of β-adrenergic mechanisms by steroids. Treatment with thromboxane synthetase inhibitor redirected eicosanoid production toward prostacyclin production. This overproduction of the vasodilator might be responsible for the aggravation of systemic hypotension but appears unable to override the pulmonary vasoconstrictor effects of other mediators besides thromboxane. Platelet activating factor might have a role in the protamine reversal syndrome, and drugs such as platelet activating factor antagonists should be tested in animal models.

Our results suggest the need for further work concerning the efficacy of steroids and inhibitors of arachidonic acid metabolism against the protamine reaction, with the eventual goal of developing therapeutic measures for preventing the complex and catastrophic reactions to protamine in human patients.

References

1. Horrow JC. Protamine: a review of its toxicity. Anesth Analg 1985;64:348–61.
2. Lakin JD, Blocker J, Strong DM, Yocom MW. Anaphylaxis to protamine sulfate mediated by a complement-dependent IgG antibody. J Allergy Clin Immunol 1978;61:102–7.
3. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation during cardiopulmonary bypass. Evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med 1981;304:497–503.
4. Morel DR, Zapol WM, Thomas SJ, et al. C5a and thromboxane generation associated with pulmonary vaso- and bronchoconstriction during protamine reversal of heparin. Anesthesiology 1987;66:597–604.
5. Westaby S, Turner MW, Stark J. Complement activation and anaphylactoid response to protamine in a child after cardiopulmonary bypass. Br Heart J 1985;53:574–6.
6. Hobbhahn J, Conzen PF, Zenker B, Goetz AE, Peter K, Brendel W. Beneficial effect of cyclooxygenase inhibition on adverse hemodynamic response after protamine. Anesth Analg 1988; 67:253–60
7. Morel DR, Lowenstein E, Nguyenduy T, et al. Acute pulmonary vasoconstriction and thromboxane release during protamine reversal of heparin anticoagulation in awake sheep: evidence for the role of reactive oxygen metabolites following nonimmunological complement activation. Circ Res 1988;62: 905–15.
8. Conzen PF, Habazettl H, Gutmann R, et al. Thromboxane mediation of pulmonary hemodynamic responses after neutralization of heparin by protamine in pigs. Anesth Analg 1989;68:25–31.
9. Blackwell GJ, Carnuccio R, DiRosa M, Flower RJ, Parente L, Persico P. Macrocortin: a polypeptide causing the antiphospholipase effect of glucocorticoids. Nature (London) 1980; 287:147–9.
10. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984;5:25–44.
11. Best N, Teisner B, Grudzinskas JG, Fisher MM. Classical pathway activation during an adverse response to protamine sulphate. Br J Anaesth 1983;55:1149–53.
12. Sander RA, Hirshman CA. Protamine-induced histamine release in human skin mast cells. Anesthesiology 1990;73:165–7.
13. Levy JH, Faraj BA, Zaidan JR, Camp VM. Effects of protamine on histamine release from human lung. Agents Actions 1989; 28:70–2.
14. Kambam J, Meszarosf R, Merrill W, Stewart J, Smith BE, Bender H. Prophylactic administration of $histamine_1$ and $histamine_2$ receptor blockers in the prevention of protamine related hemodynamic effects. Can J Anaesth 1990;37:420–2.
15. Boecklen E, Flad S, Faber HV. Hydrocortisone increases β-adrenergic receptors in rat musculus longissimus and heart. Drug Dev Res 1987;10:11–5.
16. Maguire ED, Wallis RB. In vivo redirection of prostaglandin endoperoxides into 6-keto-$PGF_{1\alpha}$ formation by thromboxane synthetase inhibitors in rat. Thromb Res 1983;32:15–21.

Transcatheter Closure of Atrial Septal Defects: Hemodynamic Complications and Anesthetic Management

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Transcatheter closure of atrial septal defects using a double-umbrella (clamshell) device can now be performed during an overnight hospital stay with little morbidity and no mortality. The initial 2-yr experience with anesthetic care for the procedure was collected and subsequently analyzed. Primary anesthetic care was given in 118 cases and urgent anesthetic intervention was required in another four cases. Anesthesia with spontaneous ventilation in patients with unprotected airways using intravenous ketamine and midazolam (average cumulative doses 1.4 and 0.17 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively) was used in 93 cases (77%); mean maximum Pa_{CO_2} value was 41 ± 6 mm Hg. In 29 patients (23%) tracheal intubation and muscle paralysis were used to facilitate control of airway and ventilation. Anesthetic-related complications occurred in three patients: ventilatory compromise developed in two patients in the spontaneous ventilation group and one patient experienced awareness during endotracheal anesthesia with paralysis. Procedural complications that altered anesthetic management were more frequent, including embolization of the clamshell device requiring surgical retrieval in two of six embolizations, intracardiac air embolization (four cases), tricuspid regurgitation (one case), device malplacement requiring late operation (one case), and transient brachial plexus injury (three cases). Anesthesia for transcatheter atrial septal defect closure allows precise device placement, prompt control of hemodynamic complications, and transesophageal echocardiographic monitoring of device placement. Although general anesthesia with spontaneous ventilation using ketamine and midazolam was usually safe and effective, tracheal intubation for control of airway and ventilation was sometimes necessary for safety and for optimal operating conditions. Familiarity with transcatheter closure techniques and close communication with the catheterization team is essential to minimize and treat associated complications. Anesthetic care is now routine practice for transcatheter closure of atrial septal defects at our institution.

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Just as adult cardiac anesthesia practice was altered by the advent of percutaneous balloon coronary angioplasty, pediatric cardiac anesthesia is changing because of a variety of interventional cardiac catheterization treatments being developed for congenital heart disease (1,2). Of these interventional techniques, transcatheter closure of atrial septal defect (ASD) may have the greatest impact on institutions doing pediatric cardiac surgery.

Transcatheter techniques for closure of ASDs have been attempted for several decades, but widespread use has been prevented by practical problems, including difficulty with device placement. Recent development of a double-umbrella device, the Bard Clamshell Septal Umbrella (USCI Angiographics, Tewksbury, Mass.), has made it feasible to close approximately two-thirds of simple ASDs at this institution in patients weighing more than 8 kg (3,4). Although currently being implanted only under research protocols approved by the Food and Drug Administration, release of this device for general clinical use is anticipated in the near future. Experience to date suggests that for most ASDs, transcatheter closure will soon become the treatment of choice (5,6).

Early experience with the technique showed that during the critical period of device placement and release, patient movement, even movement of the heart with vigorous respiration increased the likelihood of suboptimal placement, device embolization, or entrainment of air through the delivery sheath. Later experience in larger and more complex ASDs led to the use of transesophageal echocardiographic

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guidance for precise placement of the double-umbrella device (7). Because of these experiences, anesthesia has become routine for most cases, particularly in children. To evaluate and assess the anesthetic care and procedural complications occurring during transcatheter ASD closure, we have reviewed the collected data from our initial experience with anesthetic management for this new, nonsurgical procedure.

Methods

All devices were implanted under research protocols approved by the local Committee on Clinical Investigation and the Food and Drug Administration. Anesthetic records were collected starting in February 1989 and ending in December 1990 from all patients receiving anesthetic care for transcatheter closure of a secundum-type ASD or patent foramen ovale with the Clamshell Occluder. Also included were patients who had previously undergone a "fenestrated" modified Fontan procedure for various high-risk complex cardiac defects and subsequently had their ASDs (fenestrations) closed with a clamshell device (8).

Significant hemodynamic and device-related complications during and after the transcatheter ASD closure were recorded according to Food and Drug Administration and institutional protocols. Purely anesthetic complications not affecting hemodynamics were recorded on the anesthetic record. In addition, the cause and treatment of all complications occurring during the procedure were discussed at monthly catheterization laboratory complication conferences with anesthesiologists in attendance.

Patients were monitored by the anesthesia team with electrocardiogram, pulse oximetry, noninvasive automated blood pressure measurement, and end-tidal CO_2 measurement, using a nasal catheter in patients without an endotracheal tube. Independent monitoring of electrocardiogram and intermittent monitoring of intracardiac pressures and oxygenation saturation were done by the cardiology team and were available to the anesthesiologist when requested. Arterial blood pressures were monitored throughout the procedure using a femoral arterial catheter as the routine practice during interventional cardiac catheterizations in our institution. Periodic complete arterial blood gas measurements were taken in all patients. Biplane fluoroscopy of the chest and heart was immediately available for assessment of endotracheal tube and catheter positions, lung expansion, cardiac function, and location of gas, fluid, or contrast in the lungs, heart, and thoracic or pericardial cavities. At least one intravenous line was controlled by the anesthesiologist for fluid and drug infusions. Central venous and arterial access was available through the catheterization site.

The anesthetic technique used was based on intravenous midazolam and ketamine. Loading doses of 0.1–0.2 mg/kg of midazolam were given along with 0.25–0.5 mg/kg of ketamine followed by a continuous infusion of ketamine ($1\ mg \cdot kg^{-1} \cdot h^{-1}$) and midazolam ($0.1\ mg \cdot kg^{-1} \cdot h^{-1}$) supplemented by boluses when indicated. Additional intermittent boluses of both drugs were given alternatively in place of an infusion when patients became responsive or moved. When transesophageal echocardiography (TEE) was used, the patient's spontaneous respirations or movement interfered with device placement, or airway problems were anticipated, patients were paralyzed using muscle relaxants, electively intubated, and ventilated with positive pressure.

Data analysis included calculation of mean patient demographic data, mean drug dosage, maximum Pa_{CO_2}, and incidence of complications. Comparisons of mean values were done using Student's *t*-tests. Data are presented as the mean or median ± the standard deviation.

The technique of transcatheter ASD closure has been previously described (3,4) and is shown schematically in Figure 1. When the septal defect was large or located close to cardiac valves, TEE was used to determine the position of the multiple device arms on either side of the septum to assure correct positioning before device release. Subsequently, TEE with color flow Doppler was used to evaluate residual shunting or interference with normal atrioventricular valve function.

When properly placed in the defect, the spring-loaded opposing arms hold the device in place by engaging the atrial septal surface from opposite sides. The fabric mesh becomes closed by clot and the device subsequently becomes endothelialized on both sides of the septum, permanently incorporating the device into the heart (3).

Results

Table 1 shows the demographics of the patients receiving anesthetic care, including ASA status, and the distribution of diagnoses. During the 2 yr of patient accrual and data collection, 118 patients had anesthesia during transcatheter closure of one or more ASDs using the clamshell device. Atrial septal defects of various types were closed by the cardiology staff without anesthesia assistance in another 56 patients. In four of the 56 patients (7%) in whom devices were placed without anesthetic care, anesthestic assistance was urgently or emergently requested. Life-threatening complications prompted anesthetic intervention in two of these four patients.

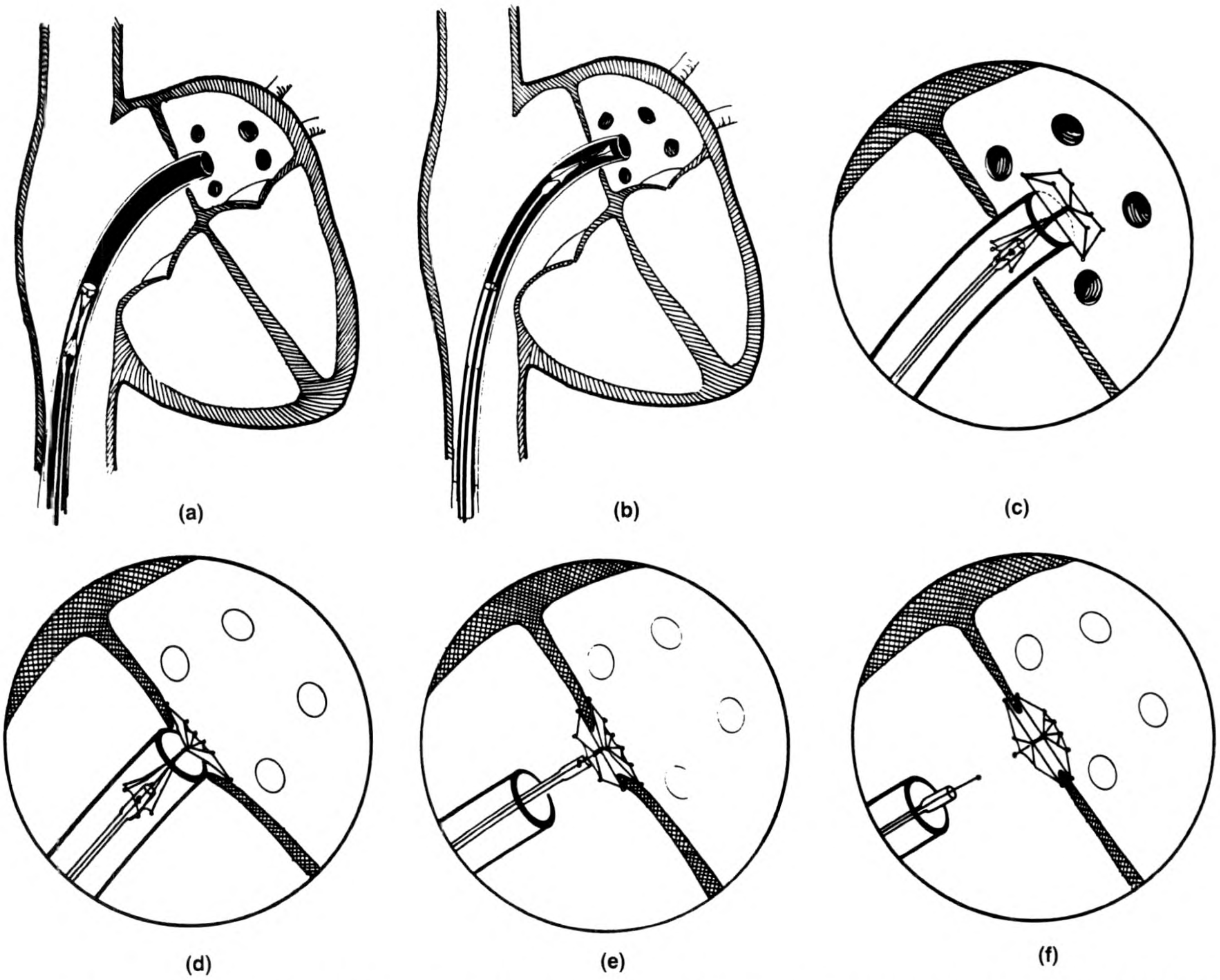

Figure 1. Technique of transcatheter ASD closure. (**a**) The collapsed clamshell device is passing through the introducer sheath. (**b**) The device and sheath as a unit are positioned on the left atrial side of the defect using previously determined fluoroscopic landmarks. (**c**) The sheath is then pulled partially back, allowing one set of flexible, spring-loaded arms (covered with Dacron mesh) to spring open in the left atrium. (**d**) The sheath, delivery system, and the half-opened clamshell device are then pulled back as a unit, until the open arms engage the left atrial septal surface. (**e**) The sheath is pulled further back to expose the proximal half of the device, allowing it to spring open and engage the right atrial septal surface. (**f**) The clamshell device is released and sits in the heart straddling the atrial septum. (Reprinted by permission of the American Heart Association, Inc. from Lock JE, Rome JJ, Davis R, et al. Transcatheter closure of atrial septal defects: experimental studies. Circulation 1989;79:1091–9.)

In the other two patients lack of patient cooperation and adequate sedation impeded device placement and anesthetic care was requested to allow completion of the procedure. The 122 cases receiving anesthetic care either initially (118) or starting at some point during the procedure (4) are analyzed in this report. No complications in the 52 cases not receiving any anesthetic care are included in the following analysis.

Table 2 lists the major anesthetic and procedure-related complications encountered, their treatment, and the outcome. There was no mortality or appreciable long-term morbidity in any patients who had transcatheter closure of an ASD in this series, including the two patients with life-threatening complications who did not initially receive anesthetic care. The immediate availability of anesthesiologists in the catheterization laboratory contributed to the prompt stabilization and good outcome in these latter two patients.

Light general anesthesia in spontaneously breathing patients with unprotected airways, using intravenous ketamine and midazolam as described above was used in 93 of 122 (77%) patients. Mean cumulative intravenous doses of midazolam and ketamine were 0.17 and 1.4 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively, administered either by periodic bolus technique or by continuous infusion following loading boluses as previously described. All patients received an antisialagogue for control of airway secretions, either glycopyrolate (10 $\mu g/kg$) or atropine (20 $\mu g/kg$). The

Table 1. Patient Information

Age (yr)	
Median	6
Mean	14
Range	0.75–77
Weight (kg)	
Mean	20
Median	32
Range	8–100
Sex[a]	
Male	56
Female	66
Diagnosis[a]	
ASD (secundum)	79
PFO	13
FF	30
ASA classification[a]	
II	70
III	46
IV	6
E	3[b]

ASD, atrial septal defect; PFO, patent foramen ovale; FF, fenestrated Fontan.

[a] Number of patients.

[b] These patients included in ASA classes III and IV.

mean maximum $Paco_2$ recorded in these patients was 41 ± 6 mm Hg; 8 of 93 (9%) patients had $Paco_2$ ≥ 50 mm Hg at some time (maximum, 57 mm Hg). Small doses of opiates (morphine or fentanyl) were used to supplement the basic anesthetic technique in half of the spontaneously breathing patients and tended to increase the maximum $Paco_2$ seen. However, the mean maximum recorded $Paco_2$ in patients receiving opiates was not significantly increased. Clinical evaluation and routine chest roentgenogram taken 3–12 h after the procedure in all patients, including those with unprotected airways, revealed no evidence of aspiration pneumonitis. Furthermore, no clinical pneumonia developed subsequently in any patient receiving anesthesia.

Tracheal intubation and controlled positive pressure ventilation with muscle paralysis was elected (or required) in 29 of 122 (23%) patients. In all but four of these cases, tracheal intubation was elected because TEE was used. Initial experience with attempts at passage and subsequent manipulation of a transesophageal echo probe in lightly anesthetized, spontaneously breathing patients with unprotected airways was unfavorable because of excessive and unpredictable patient movement and tenuous airway patency during insertion and manipulation of the transesophageal probe. Early in the experience, elective intubation was instituted for these patients. In a small number of patients, inadequate spontaneous ventilation or excessive patient movement prompted tracheal intubation and muscle paralysis. In patients whose tracheas were intubated, anesthesia and muscle paralysis was maintained for the duration of the procedure with a continuation of the intravenous agents or with supplemental inhaled anesthetics.

Ventilatory compromise requiring mask ventilation and subsequent intubation developed in two spontaneously breathing patients with unprotected airways (2%). Two other patients required paralysis, intubation, and control of ventilation because of lack of immobility or because spontaneous respirations interfered with the transcatheter ASD closure. In one patient whose trachea was electively intubated and neuromuscular blockade continued, awareness and hypertension occurred.

Procedure-related complications were more frequent and often required immediate treatment by the anesthesiologist. Systemic air embolization in particular caused dramatic but reversible hemodynamic changes (Table 2). Despite use of controlled ventilation with positive pressure in two of the four cases, sufficient amounts of air embolized into the systemic circulation to cause serious hemodynamic changes.

Tricuspid regurgitation with hemodynamic compromise occurred acutely in one case (Table 2) during placement of the device, secondary to the delivery catheter or device impinging on the valve apparatus. This responded to inotropic support and eventual repositioning of the catheter and device. In another case (Table 2), a large (40 mm) device in a small (6-yr-old) patient also impinged on the tricuspid valve, but no acute regurgitation or hemodynamic compromise resulted and the device was left in place. The device was electively removed in the operating room 7 days after placement. At the time of removal and surgical ASD repair, left atrial wall perforation by the device together with a small hemorrhagic pericardial effusion without tamponade was incidentally noted. Acute myocardial perforation with tamponade did not occur in any patient having transcatheter ASD closure.

Blood loss from the catheterization site requiring transfusion or colloid replacement was an infrequent problem, occurring in 9 of 120 (8%) patients. Although mean volume replacement was 17 mL/kg of blood or colloid, replacement requirements exceeded 30% of the total blood volume in two small children because of blood loss from the catheterization site, primarily from the large (11F) delivery sheath.

Discussion

Using a variety of surgical techniques, ASDs have been repaired since about 1953: hypothermia and inflow occlusion by Lewis and Tauffic (9), the atrial well technique by Gross et al. (10), and the pump oxygenator by Gibbon (11). After Gibbon's work, ASD repairs have been done during open heart

Table 2. Complications

Complication	Treatment	Result
Procedural complications		
Device embolization (6 cases)	Catheter retrieval (4)	ASD closed in cath. lab. No sequelae
	OR retrieval (2)	ASD closed in OR. No sequelae
	Femoral vessel repair in OR (1)	No sequelae
Air embolization (4 cases)	Pressors, atropine, volume intubation and brief CPR in one case	Transient seizure. No sequelae
Acute mitral or tricuspid regurgitation (1 case)	Pressor, inotropic support, and repositioning of catheter	No sequelae
Device impingement on tricuspid valve, asymptomatic (1 case)	Elective OR removal and ASD repair at 7 days. Perforation and small amount of free blood in pericardium at operation.	No sequelae
Brachial plexus injury (3 cases)	None	Transient, full recovery
Severe stridor and hypoventilation 2° to dye reaction (1 case)	Airway support and positive pressure ventilation	No sequelae
Blood loss requiring transfusion or colloid replacement (9 cases)	Blood transfusion (5 cases) Albumin (4 cases) Mean volume given, 17 mL/kg	Normotensive, no sequelae
Anesthetic complications		
Apnea or airway obstruction (2 cases)	Airway support and intubation	No sequelae
Awareness during general endotracheal anesthesia	None	No sequelae

OR, operating room; CPR, cardiopulmonary resuscitation; ASD, atrial septal defect; cath lab, catheterization laboratory.

surgery and cardiopulmonary bypass. The cost of ASD closure using current open heart techniques is high, although mortality and complications are very low (5,12). Surgical ASD closure requires midline sternotomy, cardiopulmonary bypass, and a 5–7-day hospital stay including intensive care. Transcatheter closure of ASDs needs only an overnight stay and has even been done as an outpatient procedure. The absence of mortality and low initial morbidity in the present series of cases compares quite favorably with surgical complications and results in complete or virtually complete closure in 95% of patients. Long-term morbidity is not known at this time.

This technique for ASD closure is likely to become the preferred procedure for the majority of ASD patients. The problems identified here, both those related to the anesthetic management itself and those related to the procedure, will concern anesthesiologists involved in congenital heart surgery when the clamshell device is released for general, noninvestigational use. In some instances, the hemodynamic effects of the procedure-related complications can approach those seen with manipulations during open heart surgery. However, the spectrum of procedure-related complications seen here is unique to this form of interventional cardiac catheterization. Prevention of complications and of their potential morbidity are both to a large extent dependent on the skill and experience of the anesthesia and catheterization team. The anesthesiologist must be prepared to treat immediately serious complications whenever they occur, in concert with the catheterization team, to prevent morbidity.

Complications related to anesthetic management were infrequent. The low incidence of ventilatory compromise requiring intubation (2%) and modest levels of hypercapnea that occurred (maximum Pa_{CO_2}, 57 mm Hg) in unconscious patients spontaneously breathing with unprotected airways is attributable to the low doses of ketamine and midazolam used, end-tidal CO_2 monitoring, careful choice of patients, and careful titration to effect by anesthesiologists. The ketamine and midazolam combination usually resulted in good conditions for transcatheter ASD closure in mostly normocarbic, immobile patients with smooth spontaneous respirations. The level of anesthesia obtained usually resulted in apparent unconsciousness but with patient movement or responsiveness in response to strong stimulation. Occasionally this technique of light general anesthesia could not provide adequate operating conditions or adequate spontaneous ventilation, particularly in the face of strong stimulation such as passage of a transesophageal echo probe. When this occurred, tracheal intubation, controlled ventilation, and paralysis became necessary or were elected before the stimulation.

As a result of this experience, we now use a combined infusion of ketamine ($1\ mg\cdot kg^{-1}\cdot h^{-1}$) and midazolam ($0.1\ mg\cdot kg^{-1}\cdot h^{-1}$) as a basal anesthetic for transcatheter ASD closure after a bolus of 0.25–0.5 mg/kg of ketamine and 0.1–0.2 mg/kg of midazolam. The reported use of higher ketamine doses alone in cardiac catheterization laboratories for both interventional (13) and diagnostic (14,15) procedures has previously resulted in a more substantial incidence of airway and ventilatory compromise ranging from 7.5% to 20%.

Although general endotracheal anesthesia was clearly required in some ASD cases and helpful in others when adequate operating conditions could not be achieved with the light general anesthesia, the advantages of general endotracheal anesthesia other than airway control for most interventional cardiac catheterization cases are unclear. In adults, use of general anesthesia during percutaneous balloon coronary angioplasty for acute myocardial infarction resulted in better arterial oxygenation and patient satisfaction than the use of conscious sedation (16). However, no outcome difference in mortality and morbidity could be demonstrated between the different types of anesthetic care in these adult patients where the spectrum of device-related complications is quite different.

Complications related to device placement were the greatest problem for the anesthesiologist, although no long-term morbidity resulted. When device embolization occurred and transcatheter retrieval was not successful, general anesthesia was induced and the patient was transferred to the operating room after a period of stabilization. Although severe hemodynamic compromise with device embolization is a potential problem, hemodynamic compromise requiring emergent transfer to the operating room did not occur in this series. A cardiac operating room therefore is not kept on standby when transcatheter ASD closures are scheduled. A related problem sometimes requiring surgical repair is femoral vessel injury when embolized devices are retrieved and removed. Nonemergent surgical repair of femoral vessels in the operating room during general endotracheal anesthesia was done in two cases. Similar complications requiring surgical exploration and repair of femoral arterial vessels occur with balloon angioplasty of systemic arterial obstructions in children (17).

In patients with an intracardiac shunt, air embolization may be life threatening. When not occupied by the carrier system and collapsed device, the large delivery sheath represents a potential space for air accumulation and subsequent delivery into the heart. In addition, when the entry port of the large delivery sheath is open during removal and reinsertion of various catheters and devices, extreme inspiratory efforts may entrain air directly into the heart and thence into the systemic circulation in these patients. Left atrial air embolization, shown by ST segment elevation and fluoroscopic visualization, occurred in all four cases of symptomatic air embolism. Serious hemodynamic changes resulted, but not demonstrable long-term sequelae. The ST segment changes, hypotension, arterial desaturation, and bradycardia seen in these cases responded to aspirating and then sealing the sheath port, along with administering atropine and inotropic and pressor support to maintain and increase coronary perfusion pressure, with simultaneous volume administration. Chest compressions were briefly required in one case but no long-term sequelae was noted even in this case of brief, but severe, hemodynamic decompensation.

Meticulous purging of air from the catheter system and sealing of open ports should minimize the incidence of air embolism, but this remains to be proven. Use of controlled positive pressure ventilation through an endotracheal tube in an anesthetized, paralyzed patient may also decrease the potential for transcatheter air entrainment with inspiratory efforts, but it did not always prevent air embolization in this series. Tracheal intubation and positive pressure ventilation are not now routinely used in these cases, but if inspiratory efforts are extreme, respiratory compromise is present, or device placement is difficult, intubation and positive pressure ventilation are prudent.

Interference with atrioventricular valve function during or after device placement was infrequent in this series, but when these devices are placed in other locations, as in closure of ventricular septal defects, interference with mitral or tricuspid valve function resulting in hemodynamic compromise is more frequent. Perforation occurred only late in one case in this series and did not result in tamponade, but myocardial perforation and acute tamponade have occurred in the catheterization laboratory with other interventional catheterization procedures.

Brachial plexus injury is a risk of interventional catheterization procedures and could arguably be classified as either an anesthetic- or procedure-related complication. Cardiologists prefer the hands positioned over and behind the head with more than 90° of upper arm abduction to allow the lateral cardiac cineangiographic and fluoroscopic views needed for precise positioning of the clamshell device. This is the classic high-risk position for brachial plexus injury. Constant vigilance and attention to repositioning are needed when cineangiography and fluoroscopy are not in use to minimize plexus stretch and compression over the humeral head. The three brachial plexus injuries in this series were transient but signal the potential in the catheterization laboratory for severe brachial plexus injury in deeply sedated or anesthetized patients.

In summary, the anesthetic goals for transcatheter ASD closure are patient comfort and safety, immobility, adequate ventilation, monitoring of hemodynamics, and provision of circulatory support so that complications and subsequent morbidity can be minimized. These goals allow the cardiologist to concentrate on the demanding technical requirements of transcatheter ASD closure. In many patients these goals can be met with a light general anesthetic that allows spontaneous breathing through an unprotected airway. In other patients, general endotracheal anesthesia with controlled ventilation may be preferable. Regardless of the anesthetic approach chosen, close communication and cooperation with the cardiology team is essential, as is knowledge of the techniques of transcatheter ASD closure and its spectrum of complications. As a result of the accumulated experience reported here, anesthetic care is now our institutional practice for all patients undergoing transcatheter closure of a secundum-type ASD or a patent foramen ovale.

References

1. Beekman RH, Rocchini AP. Transcatheter treatment of congenital heart disease. Prog Cardiovasc Dis 1989;32:1–30.
2. Perry SB, Keane JF, Lock JE. Interventional catheterization in pediatric congenital and acquired heart disease. Am J Cardiol 1988;61:109G–17G.
3. Rome JJ, Keane JF, Perry SB, Spevak PJ, Lock JE. Double-umbrella closure of atrial septal defects: initial clinical applications. Circulation 1990;82:751–8.
4. Lock JE, Rome JJ, Davis R, et al. Transcatheter closure of atrial septal defects: experimental studies. Circulation 1989;79:1091–9.
5. Borow KM, Karp R. Atrial septal defect: lessons from the past, directions for the future. N Engl J Med 1990;323:1698–700.
6. Rocchini AP. Transcatheter closure of atrial septal defects: past, present, and future. Circulation 1990;82:1044–5.
7. Hellenbrand WE, Fahey JT, McGowan FX, et al. Transesophageal echocardiographic guidance for transcatheter closure of atrial septal defect. Am J Cardiol 1990;66:207–13.
8. Bridges ND, Lock JE, Castaneda AR. Baffle fenestration with subsequent transcatheter closure: modification of the Fontan operation for patients at increased risk. Circulation 1990;82:1681–9.
9. Lewis FJ, Tauffic M. Closure of atrial septal defects with the aid of hypothermia: experimental accomplishments and the report of the one successful case. Surgery 1953;33:52.
10. Gross RE, Pomeranz AA, Watkins E Jr, Goldsmith EI. Surgical closure of defects of the interauricular septum by use of an atrial well. N Engl J Med 1952;247:455.
11. Gibbon JH. Application of a mechanical heart-lung apparatus to cardiac surgery. Minn Med 1954;37:171–85.
12. Murphy JG, Gersh BJ, McGoon MD, et al. Long-term outcome after surgical repair of isolated atrial septal defect: follow-up at 27–32 years. N Engl J Med 1990;323:1645–50.
13. Malviya S, Burrows FA, Johnston AE, Benson LN. Anaesthetic experience with paediatric interventional cardiology. Can J Anaesth 1989;36:320–4.
14. Faithful NS, Haider R. Ketamine for cardiac catheterization: an evaluation of its use in children. Anaesthesia 1971;26:318–23.
15. Coppel DL, Dundee JW. Ketamine anaesthesia for cardiac catheterization. Anaesthesia 1972;27:25–31.
16. De Bruijn NP, Hlatky MA, Jacobs JR, et al. General anesthesia during percutaneous transluminary coronary angioplasty for acute myocardial infarction: results of a randomized controlled clinical trial. Anesth Analg 1989;68:201–7.
17. Burrows PE, Benson LE, Williams WG, et al. Iliofemoral arterial complications of balloon angioplasty for systemic obstructions in infants and children. Circulation 1990;82:1697–704.

Electrocardiographic Changes During Cesarean Section Under Regional Anesthesia

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To determine electrocardiographic changes and whether myocardial ischemia occurs during cesarean section, electrocardiograms were recorded continuously using Holter monitoring in 25 patients undergoing elective cesarean section under either spinal or epidural anesthesia. In addition, in 13 of the patients, two-dimensional precordial echocardiography was carried out before and during cesarean section. ST segment depression suggestive of myocardial ischemia occurred in 16 patients including 8 of the 13 with echocardiograms. Wall motion remained entirely normal during episodes of ST segment depression. Patients in whom ST depression developed had significantly more rapid heart rates at delivery than those who did not experience ST depression. We conclude that ST segment depression is a common feature of the electrocardiogram during cesarean section under regional anesthesia and is not the result of myocardial ischemia.

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Electrocardiographic changes, which are characteristic of acute myocardial ischemia, occur during cesarean section delivery under regional anesthesia (1). Palmer et al. (1) showed that such changes developed in more than 37% of their patients and suggested that the etiology may be an imbalance of myocardial oxygen supply and demand during delivery.

Animal and human studies have shown that when myocardium becomes ischemic there is almost immediate alteration in wall motion and systolic thickening (2–7). These abnormalities can be reliably detected by two-dimensional echocardiography and have been shown to be highly sensitive and specific indicators of myocardial ischemia (8–12).

The aims of this study were, therefore, both to document the incidence of "ischemic-type" electrocardiographic (ECG) changes in patients undergoing elective cesarean section with regional anesthesia and to determine whether myocardial ischemia could be confirmed by echocardiography.

Methods

The study was approved by the local ethics committee, and all patients gave their informed consent. The patients studied were all healthy mothers undergoing elective cesarean section under regional anesthesia. Excluded were patients in ASA category III or above and those with significant hypertension (diastolic blood pressure > 100 mm Hg). The study took place in two phases. In the first phase investigation was by electrocardiography alone and in the second this was combined with echocardiography. Preoperatively, ranitidine, 150 mg, was given orally on the evening before and on the morning of surgery. Before institution of regional anesthesia, each patient was fitted with an ambulatory electrocardiogram recorder (Oxford Medilog 4000 111 two-channel system) monitoring modified V_1 and V_5 leads. An intravenous infusion was then commenced and the patient received 1 L of lactated Ringer's solution.

Epidural (0.5% plain bupivacaine) or spinal (2.5 mL of 0.5% bupivacaine in 8% dextrose) anesthesia was instituted with the patient in the sitting or lateral position, and a block was induced to a minimum level of T-6 bilaterally. Heart rate and arterial blood pressure were recorded at 1-min intervals using a 2200I Datascope. Oxygen saturation was continuously monitored. Hypotension (systolic pressure

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≤ 90 mm Hg) was treated by increasing the rate of intravenous infusion and by a 6-mg intravenous bolus of ephedrine. To compare myocardial work between the groups, the rate-pressure products were calculated before anesthesia, at skin incision, at delivery, and 5 min after delivery. Supplemental oxygen was given if oxygen saturation decreased below 98%. If additional analgesia was required after delivery, 5–10 mg of morphine was given intravenously. All significant symptoms, anesthetic and obstetric events, and their times were recorded.

Echocardiography was available in the latter half of the study and was carried out by a senior echocardiography technician. Before skin preparation and with the patient lying supine with a 15° left lateral tilt, two-dimensional precordial echocardiography was performed using a Vingmed 700 CFM. Detailed parasternal short-axis examination was carried out from base to apex. This allowed a continuous assessment of areas perfused by all three coronary arteries (13). Surgery then proceeded in the usual manner. Echocardiography was recommenced immediately after delivery and continued until there was normalization of ST segments and the patient was symptom free and hemodynamically stable.

Analysis of Data

Electrocardiogram. Ambulatory electrocardiogram tapes were decoded by the Oxford Medilog 4000 11 analyzer, and hard copy of the entire ECG tracing was obtained for analysis. For ST segment depression to be considered significant, the following criteria had to be met:

1. Electrocardiogram to have normal conduction and ST segment before the institution of regional anesthesia.
2. ST segment depression to be at least 0.1 mV at 0.08 s after the J point.
3. Changes to persist for at least 1 min (14,15).

ST elevation, T-wave changes, and arrhythmias were not regarded as specific indicators of ischemia. The configuration of the depressed ST segment (ascending, horizontal, or downsloping) was noted in each case.

Echocardiogram. Echocardiograms were reported by a cardiologist who was blinded to the patient and ECG data. The cross-sectional image at each level was assessed in detail. Normal systolic wall motion was defined as having occurred if a radius from the center of the left ventricle shortened by more than 30% with normal systolic wall thickening (9).

Statistical analysis. Statistical evaluation of the data was carried out using the Minitabs Release 7.1 statistical package. Data were analyzed by Student's t-test, χ^2-test, and Mann-Whitney U-test where appropriate. A P value of less than 0.05 was considered to be significant.

Results

Electrocardiography

Twenty-five patients were studied. Significant ST segment depression occurred in 16 of them and was only seen in the modified V_5 lead. In six cases, ST segment depression was as much as 0.2 mV; in one patient it was 0.3 mV. In three cases, the depressed ST segment was slowly ascending, in seven cases it was horizontal, and in 6 cases it was downsloping. Examples of the ECG changes are shown in Figure 1. In five patients ST depression began soon after the institution of regional anesthesia, in two patients at the beginning of surgery, and in nine patients at the time of delivery. In every case there was a marked temporal relationship between the sinus tachycardia, particularly at delivery, and an acute deviation of the ST segment (Figure 2). ST segment depression was always maximal in the first minute after delivery. The duration of ST segment depression after delivery was variable, ranging from 1 to 30 min with a mean of 7.5 min. Figure 3 illustrates the hemodynamic data. In both groups the fastest heart rates occurred at delivery. Mean heart rates were higher in the group with ST depression than in the group without ST depression, the difference becoming statistically significant at delivery (127.9 compared with 111.7 beats/min, $P < 0.05$, confidence interval 2.7–29.8). There was no significant difference in the mean systolic blood pressures between the two groups, and in both they decreased slightly at delivery. Mean rate-pressure product was greatest at delivery and, although it was higher in the group with ECG changes, the difference did not reach statistical significance (13,610 compared with 12,210). Demographic data are presented in Table 1. There was no significant difference in age or body mass index between the groups. Risk factors of ischemic heart disease (family history, smoking, hypertension, and previous oral contraceptive use) were present in those with and without ECG changes, but the differences were not significant. With the exception of two patients in the group without ST changes, all patients had symptoms of reflux at some point during pregnancy. No patient complained of reflux during delivery. ST segment changes occurred in four of the five patients with spinal anesthesia and in 12 of the 20 patients with epidural anesthesia. This was not a significant difference. All patients received oxytocin immediately after delivery, but it was not possible to separate the two

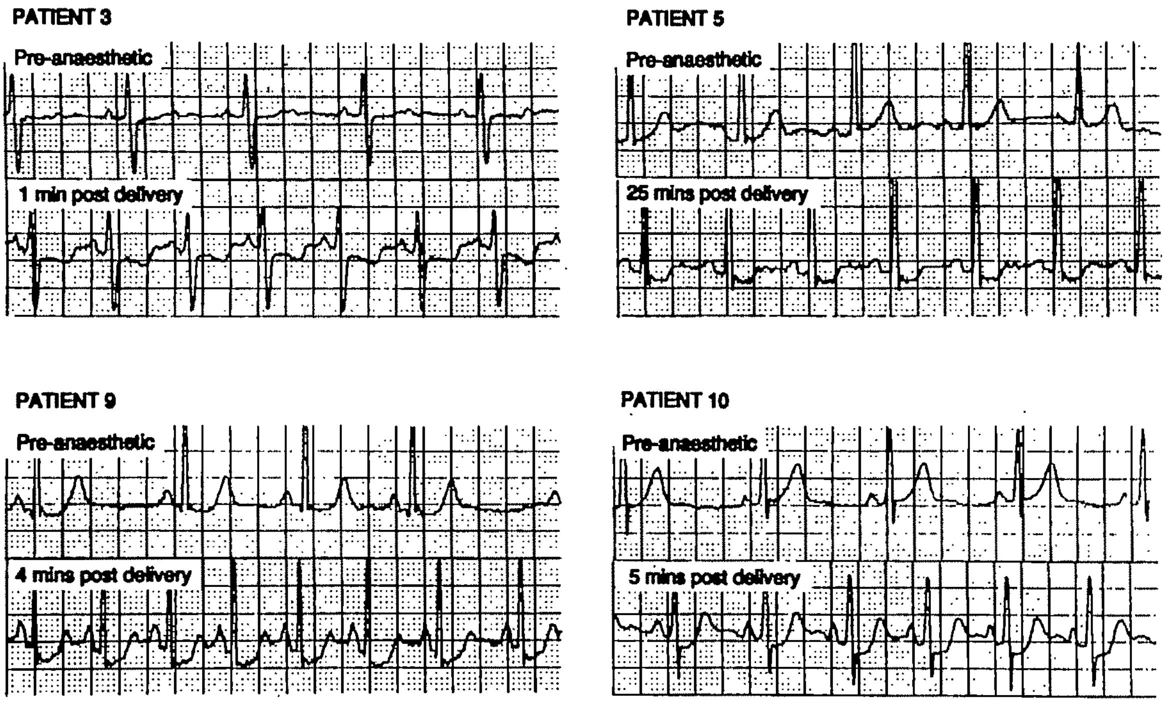

Figure 1. Examples of the electrocardiographic changes observed.

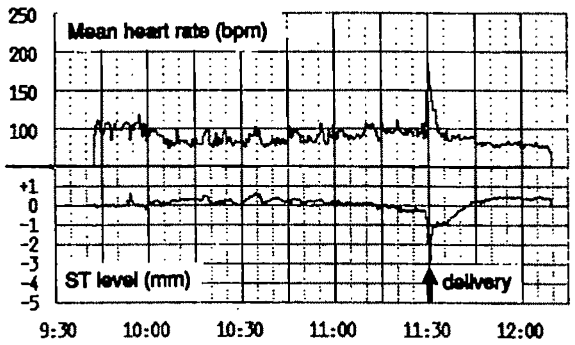

Figure 2. ST segment scan demonstrating the relationship between heart rate and ST segment depression at delivery.

events in retrospective analysis. Ephedrine was used in similar proportions in the two groups (13 of 16 patients with and 6 of 9 patients without ST depression). There were no anesthetic failures during the study. No patient complained of chest pain although two (one with and one without ST changes) described throat discomfort at the time of delivery and one (normal ST segments) had upper abdominal discomfort at peritoneal repair. Supplementary analgesia was given to these patients.

Echocardiography

Echocardiograms were obtained from 13 patients, eight of whom were subsequently found to have ST

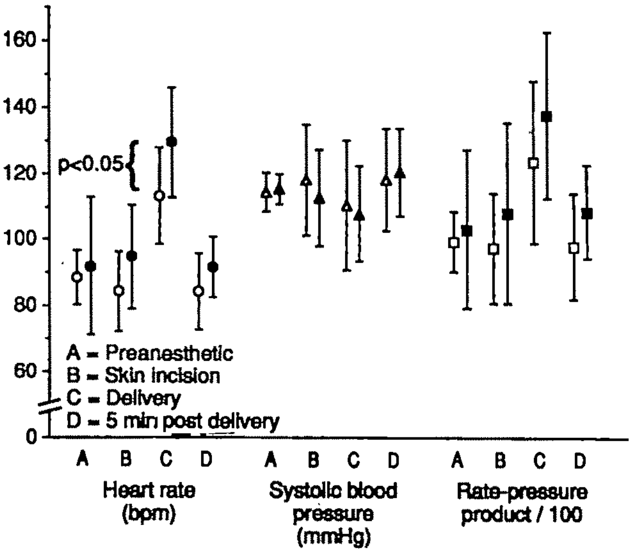

Figure 3. Changes in heart rate, systolic blood pressure, and rate-pressure product during anesthesia and cesarean section (mean ± SD). *Filled symbols,* ST segment depression; *open symbols,* no ST segment depression.

depression. In all patients the images were of excellent quality and all segments were fully visualized during the episodes of ST depression. Wall motion was normal preoperatively and remained completely normal throughout the intraoperative investigation in every case. In six patients (three with and three without ST changes) there was a trivial degree of

Table 1. Demographic Characteristics

	No. of patients	Mean age (yr)	Body mass index[a]
All patients	25	29.0 ± 4.7	37.2 ± 5.0
ST segment depression	16	29.6 ± 5.5	37.5 ± 4.8
No ST segment depression	9	27.9 ± 2.7	36.7 ± 5.8

Values are mean ± SD.

[a] Body mass index = weight (kilograms) divided by height (meters).

mitral valve prolapse. An interesting additional feature was the presence of a small amount of hemodynamically insignificant pericardial fluid in seven patients. Four of these patients had ST segment changes and three did not.

Discussion

Our study confirms that ischemic-type ECG changes are a common feature in patients undergoing cesarean section under regional anesthesia. In the detection of ST segment abnormality, ambulatory electrocardiography proved to be an ideal system as it provided a continuous record while still allowing patient movement. The modified V_5 lead was selected as it has been shown to be the most sensitive lead for the detection of ST segment abnormality (14). The V_1 lead was chosen, both for its ability to demonstrate P waves clearly (so allowing tachycardias to be identified) and to monitor anterior changes. By monitoring only two leads rather than 12, there is likely to have been some loss of sensitivity in the detection of abnormality. A fixed multilead system would, however, have reduced freedom of movement, increased the chance of artifact from lead or electrode displacement, and probably promoted patient apprehension. As it turned out, the pick-up rate with the chosen system was high, and significant ECG changes were found to be present in 16 of the 25 patients In a different population group, the assumption would be that these changes were ischemic until proven otherwise. Ischemic heart disease in women of this age group is very rare. Armstrong et al., in the Edinburgh community survey of 1972, put the incidence of myocardial infarction or probable myocardial infarction in women aged 30–44 yr (an older age group than in our study) at 0.19 per 1000 (16). The incidence of prolonged ischemic pain without infarction in the same study was 0.21 per 1000. Not surprisingly, sudden cardiac death in pregnancy is also rare. This is borne out in the reports of the Confidential Enquiries into Maternal Deaths. In the last triennium the incidence of death associated with coronary artery disease was only 2.7 per million (17). Myocardial infarction in pregnancy, has, however, been reported fairly regularly over the years and, in a literature review of the period 1922–1983, Hankins et al. identified 68 cases with an overall mortality of 37% (18). At least two of these patients had normal coronary vessels (19). Several subsequent reports have also demonstrated that peripartum myocardial infarction can occur in the absence of coronary artery disease (20–23). The mechanisms that have been proposed to account for this phenomenon include coronary spasm, small-vessel disease, hypercoagulability, and surges in myocardial oxygen demand (1,20,24,25).

Myocardial ischemia is, therefore, an uncommon but well-documented cause of morbidity and mortality in pregnancy and can occur in the absence of coronary artery disease. Because of this and the classical nature of the ST segment depression, we believed that further investigation was warranted to determine whether the ECG changes were associated with more objective evidence of myocardial ischemia. In the second phase of the study, therefore, patients underwent two-dimensional echocardiography in addition to the Holter monitoring. Echocardiographic assessment of segmental wall motion is an extremely sensitive method of detecting myocardial ischemia, and it has been suggested that it is more sensitive than the electrocardiogram in this context (10–12). The sensitivity is, of course, dependent on the production of high-quality images of both ventricles, and we were pleased that this could be achieved without difficulty. The results show that the ECG changes were not associated with any wall motion abnormalities and, therefore, could not have been due to myocardial ischemia.

Ambulatory electrocardiographic studies of healthy patients have shown that intermittent ST segment depression is a common feature of the ECG in the normal population (26–28). It is more common in women than men and, during stress testing, frequently leads to false-positive diagnoses of myocardial ischemia (29). Quyyumi et al. have also shown that ST depression in healthy patients often occurs in association with tachycardia (27). This would be consistent with the finding in our own study that those in whom ST depression developed had faster heart rates than those in whom it did not develop. The relationship between ST depression and heart rate was particularly evident at delivery and may point toward a rate-related mechanism in the production of the ECG changes. The mechanism of rate-related ST depression is yet to be established but is probably related to the production of abnormally short, steeply sloping ventricular action potentials. This leads to abnormal ventricular repolarization with deviation of the ST segment from baseline (30).

Although there was a significant difference in mean heart rate at delivery between those with and without ST depression, the wide range of heart rates within each group suggests that other factors must also have been involved in the production of the ECG changes. Mitral valve prolapse was present in only three patients with ST changes and, therefore, was not a significant contributory factor. Similarly, as ST depression occurred during spinal as well as epidural anesthesia, bupivacaine toxicity could not have been responsible for the ECG changes. There are, however, several physiologic changes that may lead to ST depression in the normal patient. Of these, anxiety, hyperventilation, alteration in posture, and changes in autonomic tone are commonplace during cesarean section under regional anesthesia, and any could have contributed to the production of the ST changes (14,26,31–33). The mechanism by which such factors may produce ST segment depression is unknown, and we can only speculate whether any were important in producing the ECG changes in our study. Further investigation is required, not only along these lines, but also to determine whether the ECG changes are specifically related to cesarean section under regional anesthesia or whether they occur in other obstetric circumstances as well.

In summary, ST segment depression occurs in a large proportion of patients undergoing elective cesarean section under regional anesthesia. The results of this study show that the ECG changes are not due to myocardial ischemia and underline the view that ST depression is a nonspecific finding in this population group. We have not identified the cause of the ECG changes, but the relationship between ST depression and heart rate suggests that it may, at least in part, be a rate-related phenomenon.

References

1. Palmer CM, Norris MC, Giudici MC, Leighton BL, DeSimone CA. Incidence of electrocardiographic changes during cesarean delivery under regional anesthesia. Anesth Analg 1990;70:36–43.
2. Tennant R, Wiggers CJ. The effect of coronary occlusion on myocardial contraction. Am J Physiol 1935;112:351–61.
3. Kerber RE, Marcus ML, Ehrhardt J, Wilson R, Abboud FM. Correlation between echocardiographically demonstrated segmental dyskinesis and regional myocardial perfusion. Circulation 1975;52:1097–104.
4. Vatner SF. Correlation between acute reductions in myocardial blood flow and function in conscious dogs. Circ Res 1980;47:201–7.
5. Gallagher KP, Kumada T, Koziol JA, McKown MD, Kemper WS, Ross J Jr. Significance of regional wall thickening abnormalities relative to transmural myocardial perfusion in anesthetised dogs. Circulation 1980;62:1266–74.
6. Battler A, Froelicher VF, Gallagher KP, Kemper WS, Ross J Jr. Dissociation between regional myocardial dysfunction and ECG changes during ischemia in the conscious dog. Circulation 1980;62:735–44.
7. Pandian NG, Kieso RA, Kerber RE. Two-dimensional echocardiography in experimental coronary stenosis. II. Relationship between systolic wall thinning and regional myocardial perfusion in severe coronary stenosis. Circulation 1982;66:603–11.
8. Pandian NG, Kerber RE. Two-dimensional echocardiography in experimental coronary stenosis. I. Sensitivity and specificity in detecting transient myocardial dyskinesis: comparison with sonomicrometers. Circulation 1982;66:597–602.
9. Smith JS, Cahalan MK, Benefiel DJ, et al. Intraoperative detection of myocardial ischemia in high-risk patients: electrocardiography versus two-dimensional transesophageal echocardiography. Circulation 1985;72:1015–21.
10. Wohlgelernter D, Jaff CC, Cabin HS, Yeatman LA, Cleman M. Silent ischemia during coronary occlusion produced by balloon inflation: relation to regional myocardial dysfunction. J Am Coll Cardiol 1987;10:491–8.
11. Visser CA, David GK, Kan G, et al. Two-dimensional echocardiography during percutaneous transluminal coronary angioplasty. Am Heart J 1986;11:1035–41.
12. Ryan T, Vasey CG, Presti CF, O'Donnell JA, Feigenbaum H, Armstrong WF. Exercise echocardiography: detection of coronary artery disease in patients with normal left ventricular wall motion at rest. J Am Col Cardiol 1988;11:993–9.
13. Fiegenbaum H. Echocardiography. 4th ed. Philadelphia: Lea & Febiger, 1986:467–9.
14. Leclerq JF, Coumel PH. Ambulatory electrocardiogram monitoring. In: MacFarlane P, Lawrie VL, eds. Comprehensive electrocardiology. Theory and practice in health and disease. New York: Pergamon, 1989:1063–106.
15. Sheffield LT. Exercise stress testing. In: Braunwald E, ed. Heart disease—a textbook of cardiovascular medicine. 3rd ed. Philadelphia: WB Saunders, 1988:229.
16. Armstrong A, Duncan B, Oliver MF, et al. Natural history of acute coronary heart attacks. A community study. Br Heart J 1972;34:67–80.
17. Turnbull A, Tindal VR, Beard RW, et al. Confidential enquiries into maternal deaths in England and Wales 1982–1984. London: HMSO, 1989.
18. Hankins GDV, Wendel GD, Leveno KJ, Stoneham J. Myocardial infarction during pregnancy: a review. Obstet Gynecol 1985;65:139–46.
19. Sasse L, Wagner R, Murray FE. Transmural myocardial infarction during pregnancy. Am J Cardiol 1975;35:448–52.
20. Cohen WR, Steinman T, Patsner B, Snyder D, Satwicz P, Monroy P. Acute myocardial infarction in a pregnant woman at term. JAMA 1983;250:2179–81.
21. Bornstein A, Dalal P, Tischler J, Novack S, Michaelson S. Acute myocardial infarction in a thirty-six year old postpartum female. Angiology 1984;35:591–4.
22. Trantom TJ, Sidhu H, Adgey AA. Myocardial infarction in pregnancy. Int J Cardiol 1988;18:35–9.
23. Sonel A, Erol C, Oral D, Omurlu K, Akyol T, Kaymakcalan S. Acute myocardial infarction and normal coronary arteries in a pregnant woman. Cardiology 1988;75:218–20.
24. Oliver MF. Ischaemic heart disease in young women. Br Med J 1974;4:253–9.
25. Glancy DL, Marcus ML, Epstein SE. Myocardial infarction in young women with normal coronary arteriograms. Circulation 1971;44:495–502.
26. Armstrong WF, Jordan JW, Morris SN, McHenry PL. Prevalence and magnitude of S-T segment and T wave abnormalities in normal men during continuous ambulatory electrocardiography. Am J Cardiol 1982;49:1638–42.
27. Quyyumi AA, Wright C, Fox K. Ambulatory electrocardiographic ST segment changes in healthy volunteers. Br Heart J 1983;50:460–4.
28. Bjerregaard P. Prevalence and magnitude of ST segment and T-wave abnormalities in healthy adult subjects during continuous ambulatory electrocardiography. In: Marchesi C, ed. Ambulatory monitoring: cardiovascular system and allied applications. The Hague: Nijhoff, 1984:114–8.

Pregnancy Does Not Alter the Threshold for Lidocaine-Induced Seizures in the Rat

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Although altered effects of various anesthetics have been demonstrated during pregnancy, published studies have incompletely defined potential pregnancy-induced changes in the central nervous system toxicity of lidocaine. Accordingly, the seizure threshold for lidocaine was measured in three groups of mechanically ventilated rats breathing 70% N_2O–30% O_2: male (n = 21), nonpregnant female (n = 19), and pregnant female (n = 23). Lidocaine was administered intravenously at a constant rate of 2.3 $mg \cdot kg^{-1} \cdot min^{-1}$ while the electroencephalogram was monitored continuously. Total doses of lidocaine and the durations of lidocaine infusion necessary to induce seizure activity were similar among groups. Plasma lidocaine concentrations at the onset of electroencephalographic seizure activity were also similar among groups (male = 10.7 ± 5.5, nonpregnant female = 12.1 ± 4.9, pregnant female = 10.8 ± 4.1 μg/mL). In a subset of each group, brain lidocaine concentrations at the onset of seizure activity were also measured, and again no differences among groups were observed (male = 17.4 ± 6.3, nonpregnant female = 16.8 ± 4.5, pregnant female = 16.7 ± 4.2 μg/100 g wet wt). The authors conclude that there are no pregnancy-specific alterations in either plasma or brain concentration thresholds for central nervous system toxicity of lidocaine in rats.

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Because of the many physiologic changes associated with pregnancy, interest has emerged regarding potential pregnancy-induced alterations in sensitivities to anesthetics. One such anesthetic, lidocaine hydrochloride, is commonly administered in large doses to obstetric patients. Although a large margin of safety is normally attributed to this drug, signs of toxicity do occur occasionally. Classically, changes in mental status precede convulsive activity, which is followed by respiratory and cardiovascular collapse. In an earlier report, Ravindran et al. (1) observed that pregnancy reduced the intraperitoneal dose of lidocaine necessary to elicit convulsive activity in mice. Conversely, we have observed in nonconcurrently studied male and pregnant female rats that the plasma lidocaine concentration necessary to elicit electroencephalographic evidence of seizure activity was 46% greater in pregnant rats than in male rats (2). Finally, Morishima et al. (3) have observed in pregnant sheep that the plasma lidocaine concentrations necessary to induce convulsive activity, as well as circulatory collapse, were very similar to those in historical nonpregnant controls. Because of these disparate results, as well as limitations in interpreting these results owing to the use of nonconcurrent control subjects, the following study was performed.

Methods

With approval from the University of Iowa Animal Care and Use Committee, three groups of Sprague-Dawley rats (Amitech, Omaha, Neb.) weighing between 300 and 400 g were studied. Age-matched male, nonpregnant female, and pregnant female (third trimester of a timed 21-day pregnancy) rats were anesthetized with 4% halothane in O_2. Lidocaine (0.5 mg) was injected subcutaneously over the trachea. A tracheostomy was performed and mechanical ventilation was begun using a small animal ventilator (tidal volume 2.5 mL, respiratory rate 33–55 breaths/min). Anesthesia was maintained with 0.8% halothane in 30% O_2/balance N_2O. Lidocaine (0.5 mg) was injected subcutaneously in the groin region, and femoral arterial and venous catheters were surgically implanted. The arterial catheter was connected to a pressure transducer for moni-

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Table 1. Physiologic Values Measured at Baseline (before lidocaine infusion) and at the Onset of Seizures

	Male ($n = 21$)	Nonpregnant female ($n = 19$)	Pregnant female ($n = 23$)
Body weight (g)	370 ± 23[a,b]	346 ± 21[a]	351 ± 39[b]
Preinfusion			
MAP (mm Hg)	127 ± 12[b]	119 ± 18	114 ± 15[b]
Pao$_2$ (mm Hg)	104 ± 15	102 ± 23	100 ± 13
Paco$_2$ (mm Hg)	41.6 ± 2.0	39.8 ± 3.2	41.0 ± 2.7
Arterial pH	7.41 ± 0.03	7.41 ± 0.04	7.39 ± 0.03
Rectal temperature (°C)	37.4 ± 0.5	37.5 ± 0.5	37.1 ± 0.6
Onset of seizures			
MAP (mm Hg)	101 ± 26[a,b]	82 ± 25[a]	85 ± 17[b]
Pao$_2$ (mm Hg)	97 ± 13	98 ± 20	95 ± 15
Paco$_2$ (mm Hg)	42.5 ± 4.6	40.3 ± 3.9	41.1 ± 4.3
Arterial pH	7.42 ± 0.04	7.42 ± 0.05	7.40 ± 0.04
Hematocrit (%)	40 ± 2[b]	41 ± 3[c]	34 ± 3[b,c]
Rectal temperature (°C)	37.5 ± 0.5	37.5 ± 0.5	37.2 ± 0.6

MAP, mean arterial blood pressure; Pao$_2$, partial pressure of oxygen in arterial blood; Paco$_2$, partial pressure of carbon dioxide in arterial blood. Values are mean ± SD.

[a] $P < 0.05$: male versus nonpregnant female.

[b] $P < 0.05$: male versus pregnant female.

[c] $P < 0.05$: nonpregnant female versus pregnant female.

toring of mean arterial pressure (MAP), and venous access was maintained for fluid and drug administration. Electroencephalographic needle electrodes were subcutaneously positioned rostral to the ears with a ground electrode placed in the midline of the scalp. D-tubocurarine (0.6 mg) and heparin (100 USP) were administered intravenously. Total surgical time was limited to 30 min. Forty-five minutes after induction of anesthesia, the halothane was discontinued and ventilation was maintained with 30% O_2–70% N_2O. Arterial blood gas/pH analyses were performed at 30, 45, and 50 min from the time of induction, with the ventilator adjusted to maintain Pao$_2$ between 70 and 120 mm Hg and Paco$_2$ between 38 and 42 mm Hg. Rectal temperature was maintained between 37 and 38°C with the use of a heating pad.

A solution of 1.5% lidocaine was prepared by diluting 2.0% Xylocaine (Astra, Westborough, Me.) in 0.9% NaCl. Sixty minutes after induction of anesthesia, a continuous intravenous infusion of this solution was started and maintained at the rate of 2.3 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ in all rats (pilot studies had indicated that this infusion regimen would typically induce seizure activity within 10–20 min). The electroencephalogram was continuously monitored beginning 5 min before the onset of lidocaine infusion. At the onset of electroencephalographic seizures, marked by the appearance of high-voltage spike wave activity, blood (5 mL) was withdrawn from the arterial catheter for blood gas/pH, hematocrit, and plasma lidocaine analysis. In a subset of rats randomly selected from each group ($n = 6$ per group), the brains were also rapidly removed at onset of seizures and frozen for later analysis. Mean arterial pressure, rectal temperature, total amount of lidocaine administered (milligrams per kilogram), and duration of lidocaine infusion were recorded at the onset of seizure activity. Plasma lidocaine concentrations were determined by gas chromatography. Frozen brains were thawed and weighed. Homogenates were made from the whole brain, and brain lidocaine was extracted and analyzed according to Levine et al. (4).

Data were analyzed by a one-way analysis of variance using the post hoc Fischer PLSD test when indicated by a significant F ratio. All results are expressed as mean ± SD. Statistical significance was assumed if $P < 0.05$.

Results

The experimental protocol was performed in 21 male, 19 nonpregnant female, and 23 pregnant female rats. Physiologic values recorded before the onset of lidocaine infusion (baseline) as well as at the onset of seizures are reported in Table 1. Body weight was significantly greater in male rats compared with either of the female groups ($P < 0.02$). Baseline values were similar among groups for Pao$_2$, Paco$_2$, arterial pH, and rectal temperature. Mean arterial blood pressure was significantly less in the pregnant female versus male group ($P < 0.05$). At onset of seizures, MAP was significantly greater in the male group ($P < 0.01$) than in either of the two female groups, which were not different from each other. Arterial blood gases and rectal temperature were not different

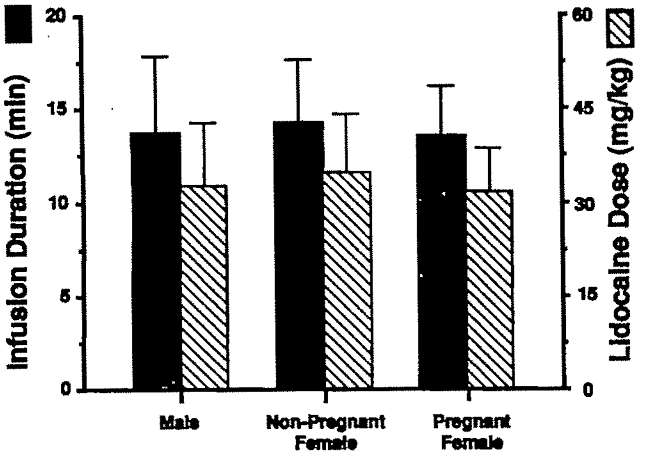

Figure 1. Mean ± SD duration of infusion and total dose of lidocaine administered at onset of seizure activity in male ($n = 21$), nonpregnant female ($n = 19$), and pregnant female rats ($n = 23$).

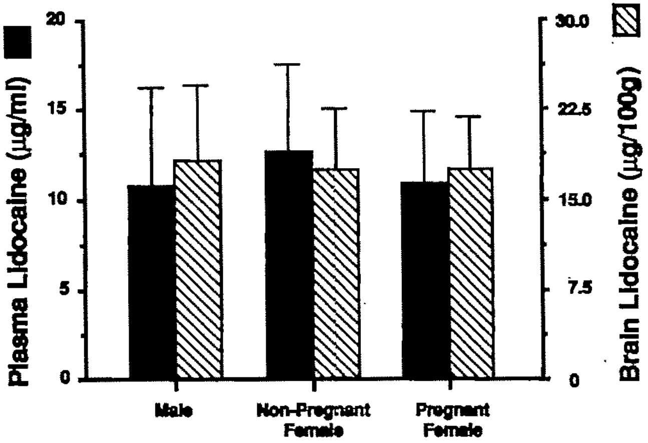

Figure 2. Mean ± SD plasma and brain (micrograms per 100 g wet weight) lidocaine concentrations at the onset of seizure activity. Brain values were obtained in subsets of rats ($n = 6$ per group) randomly chosen from each of the three groups.

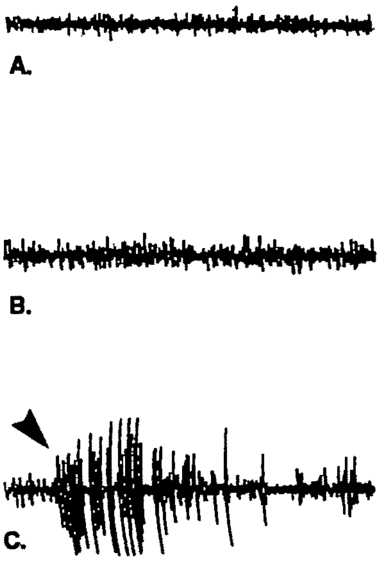

Figure 3. Electroencephalographic tracings during an experiment: (A) demonstrates typical electroencephalographic activity before the start of lidocaine infusion (during nitrous oxide analgesia) while tracing (B) occurred during the lidocaine infusion, but before the onset of seizure activity. Tracing (C) illustrates the abrupt onset of seizure activity (*arrow*).

among groups. Hematocrit was lower in pregnant female rats ($P < 0.001$).

The mean ± SD lidocaine infusion times (male = 13.7 ± 4.2, nonpregnant female = 14.3 ± 3.4, pregnant female = 13.6 ± 2.6 min) and the total dose of lidocaine administered to elicit seizures (male = 32.7 ± 4.2, nonpregnant female = 34.2 ± 8.3, pregnant female = 31.6 ± 6.2 mg/kg) were similar among the three groups (Figure 1). There were no statistically significant differences among groups for mean lidocaine concentrations in either the plasma (male = 10.7 ± 5.5, nonpregnant female = 12.1 ± 4.9, pregnant female = 10.8 ± 4.1 µg/mL) or brain (male = 17.4 ± 6.3, nonpregnant female = 16.8 ± 4.5, pregnant female = 16.7 ± 4.2 µg/100 g wet wt) at the onset of seizure activity (Figure 2). Figure 3 demonstrates a typical electroencephalographic recording during an experiment.

Discussion

Numerous investigations have identified pregnancy-induced alterations in anesthetic potency. For example, the minimal alveolar concentration for halothane is decreased by 25% in pregnant sheep, and by 40% for isoflurane (5). Laboratory studies have associated this effect with increases in plasma progesterone concentrations, although the neural basis for such an effect remains speculative (6). Exaggerated responses to intrathecally and epidurally administered local anesthetic agents during pregnancy have also been reported (7,8). These latter effects may in part be attributable to a reduction in the size of the epidural and intrathecal compartments during pregnancy, although this does not explain the increased sensitivity to intraspinal anesthetics during the first trimester of pregnancy (7). Other evidence suggests a direct effect of pregnancy that increases peripheral nervous system sensitivity to both bupivacaine and lidocaine (9–11).

Consistent with these effects of pregnancy in the peripheral nervous system is some evidence that pregnancy also alters the potency of local anesthetic agents in the central nervous system. Morishima et al. (12) reported that the plasma bupivacaine concentration necessary to cause convulsions tended to be reduced in pregnant sheep, although this effect did not achieve statistical significance. More importantly, when the bupivacaine infusion was continued in the same animals until cardiovascular collapse occurred, brain concentrations of bupivacaine were nearly twofold greater in pregnant versus nonpregnant subjects. Interestingly, similar pregnancy-induced effects on mepivacaine central nervous system toxicity could not be identified (13). In the latter study, the protein binding of bupivacaine and mepivacaine were measured in the serum of pregnant and nonpregnant sheep. Whereas pregnancy had no effect on the fraction of mepivacaine that was protein-bound, bupivacaine binding was reduced by about 30% in pregnant animals. Thus, for a standard dose of bupivacaine, more unbound drug will be available to nervous tissue in the pregnant animal. This difference as well as any pregnancy-induced alterations in sensitivity to bupivacaine at the neuronal level could explain the altered potency of bupivacaine under such circumstances.

In the present study we observed no differences in total dose of intravenous lidocaine required to elicit seizures in male, nonpregnant female, and pregnant female rats. These findings differ from those of Ravindran et al. (1), who demonstrated a lower seizure threshold in pregnant mice than in nonpregnant mice after intraperitoneal administration of lidocaine. Measurement of plasma lidocaine concentrations might have clarified whether their results were attributable to a difference in absorption after intraperitoneal administration, or whether there was a true difference in seizure thresholds between pregnant and nonpregnant mice.

Morishima et al. (12) have measured the threshold for both central nervous system and cardiovascular lidocaine toxicity in pregnant ewes and compared their results with historical nonpregnant controls. Like the present study, they noted similar mean plasma lidocaine concentrations at the onset of seizure activity in both groups, and cardiovascular toxicity was similarly unaffected. Brain lidocaine concentrations were not measured. In that report it was speculated that because protein binding of lidocaine in nonpregnant and pregnant sheep may be similar, no pregnancy-specific effects on toxicity would be expected. To our knowledge the effects of pregnancy on protein binding of lidocaine have not been reported. However, because we have observed no differences in either the plasma or brain concentrations of lidocaine at onset of seizure activity, we would predict that no differences in bioavailability would be seen. This speculation, however, does not address the reported increase in neural sensitivity to lidocaine in pregnant patients undergoing a median nerve block (11). This route of administration might bypass most physiologic and anatomic changes associated with pregnancy and thus test direct effects of the agent at the neuronal level in the peripheral nervous system. Such a direct test of the sensitivity of central nervous tissue to lidocaine has not been performed but might be achieved in vitro with brain slice preparations.

Some physiologic differences among our groups were evident at the onset of seizure activity. As expected, hematocrit was significantly reduced in the pregnant female group. We are unable to explain the relative hypotension in both female groups when compared with the male group at onset of seizures, although the pregnant female group also exhibited this pattern at onset of lidocaine infusion. We do believe, however, that the observed differences in MAP were unimportant. First, all recorded blood pressures remained within a range where cerebral autoregulation would be expected to persist, and thus cerebral perfusion most likely was similar among groups. Second, blood pressure differences were absent between the pregnant and nonpregnant female groups at onset of seizures and thus should not have obscured any pregnancy-specific effects on the seizure threshold for lidocaine.

It is worthwhile to note that our rats were immobilized and ventilated with 30% O_2–70% N_2O during the infusion of lidocaine. By the time of seizure onset, halothane had been discontinued for approximately 25 min. However, it is unlikely that the animals were stressed at the onset of seizures owing to the relatively low MAP observed at that measurement interval. In a post hoc study of 10 male rats (using the same protocol), we measured the end-tidal halothane concentration 10 min after onset of lidocaine infusion (i.e., when the earliest seizures were recorded). End-tidal halothane concentration was 0.05% ± 0.04%. This concentration of halothane was unlikely to have interacted with seizure thresholds. In contrast, N_2O has been shown to elevate the lidocaine seizure threshold by about 50% in the cat (14). However, this was a constant across all groups. Because hypercapnia (which would be expected to accompany large systemic doses of lidocaine) has also been shown to alter lidocaine seizure thresholds (15), we opted for mechanical ventilation which allowed control of the background anesthetic and ventilatory state across all groups considered.

In conclusion, the seizure threshold for lidocaine was prospectively assessed in male, nonpregnant female, and pregnant female rats. Mean lidocaine doses, as well as plasma and brain concentrations of the drug at the onset of electroencephalographic seizure activity were not different among groups. These results indicate no sex- or pregnancy-specific changes in susceptibility to lidocaine-induced central nervous sytem toxicity and are consistent with previous investigations in sheep.

References

1. Ravindran RS, Kim KC, Baldwin SJ. The effect of pregnancy on the threshold to local anesthetic induced convulsions in mice. Anesthesiology 1982;57:A400.
2. Choi WW, Warner DS, Monahan DJ, Todd MM. Effects of acute hypermagnesemia on the threshold for lidocaine-induced seizures in the rat. Am J Obstet Gynecol 1991;164: 693–7.
3. Morishima HO, Finster M, Arthur GR, Covino BG. Pregnancy does not alter lidocaine toxicity. Am J Obstet Gynecol 1990; 162:1320–4.
4. Levine B, Blanke R, Valentour J. Gas chromatographic analysis of lidocaine in blood and tissue. J Analytical Toxicol 1983;7: 123–4.
5. Palahniuk RJ, Shnider SM, Eger EI. Pregnancy decreases the requirement for inhaled anesthetic agents. Anesthesiology 1974;41:82–3.
6. Datta S, Migliozzi RP, Flanagan HL, Krieger NR. Chronically administered progesterone decreases halothane requirements in rabbits. Anesth Analg 1989;68:46–50.
7. Fagraeus L, Urban B, Bromage P. Spread of epidural analgesia in early pregnancy. Anesthesiology 1983;58:184–7.
8. Bromage P. Continuous lumbar epidural analgesia for obstetrics. Can Med Assoc J 1961;85:1136–40.
9. Datta S, Lambert DH, Gregus J, Gissen AJ, Covino BG. Differential sensitivities of mammalian nerve fibers during pregnancy. Anesth Analg 1983;62:1070–2.
10. Flanagan HL, Datta S, Lambert DH, Gissen AJ, Covino BG. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 1987;66: 123–6.
11. Butterworth JF, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. Anesthesiology 1990; 72:962–5.
12. Morishima HO, Pedersen H, Finster M, et al. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63:134–9.
13. Santos AC, Pedersen H, Harmon TW, et al. Does pregnancy alter systemic toxicity of local anesthetics? Anesthesiology 1989;70:991–5.
14. DeJong RH, Heavner JE, DeOlivera LF. Nitrous oxide elevates local anesthetic seizure threshold. Exp Neurol 1972;35:558–64.
15. DeJong RH, Wagman IH, Prince DA. Effects of carbon dioxide on the cortical seizure threshold to lidocaine. Exp Neurol 1967;17:221–32.

Effect of Ropivacaine and Bupivacaine on Uterine Blood Flow in Pregnant Ewes

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The effects of ropivacaine, a new amide local anesthetic, on uterine blood flow and fetal well-being were compared with those of bupivacaine in 10 chronically instrumented pregnant ewes. In random sequence, animals received two intravenous infusions of each drug. The low infusion rate regimens were chosen to result in clinically relevant maternal plasma concentrations of local anesthetics, whereas the more rapid rates of infusions were given to assess the safety of higher maternal drug concentrations. An epinephrine infusion was given to demonstrate the appropriateness of the animal model for the measurement of uterine blood flow. Maternal and fetal heart rates, arterial blood pressure, and the ewe's central venous pressure, intraamniotic pressure, and uterine blood flow were recorded continuously. Arterial blood samples were taken from mother and fetus at frequent intervals to determine acid-base status and local anesthetic concentrations. A total of 39 studies were performed. None of the infusions of either local anesthetic resulted in a significant decrease in uterine blood flow or deterioration in fetal condition. The mean maternal plasma concentrations at the end of infusions were as follows: ropivacaine low dose, 1.60 ± 0.35 μg/mL; bupivacaine low dose, 1.55 ± 0.15 μg/mL; ropivacaine high dose, 2.50 ± 0.37 μg/mL; and bupivacaine high dose, 1.83 ± 0.19 μg/mL. Epinephrine infusion resulted in a 25% decrease in uterine blood flow without adverse fetal effects. We conclude that neither ropivacaine nor bupivacaine, as administered in this study, led to any ill effects on uterine artery blood flow or fetal well-being.

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The adequacy of the uteroplacental circulation, which may be influenced by drugs or anesthetic procedures, is an important determinant of fetal well-being. In pregnant sheep, high blood concentrations of amide local anesthetics reduce uteroplacental perfusion by causing uterine artery vasospasm and by stimulating myometrial contractility (1). Human uterine artery segments, obtained at cesarean hysterectomy, constrict with high concentrations of lidocaine and mepivacaine (2,3).

Ropivacaine, a new amide local anesthetic structurally related to mepivacaine and bupivacaine, may be useful for obstetric anesthesia. Its potency and duration of action are similar to those of bupivacaine but its therapeutic index may be larger (4–9). Furthermore, the systemic toxicity of ropivacaine in sheep, unlike that of bupivacaine, is not enhanced by pregnancy (10,11).

Ropivacaine appears to be unique among the amide local anesthetic agents in that it can produce cutaneous vasoconstriction after intradermal injection (12). Accordingly, we determined whether ropivacaine also acts as a uterine vasoconstrictor.

Methods

Time-dated pregnant sheep, at 125–130 days of gestation (term, 148 days), were studied according to a protocol approved by the Institutional Animal Care and Use Committee. Details of surgical preparation have been described previously (13). Briefly, after an

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overnight fast, ewes were given spinal anesthesia with 12–14 mg of tetracaine hydrochloride, supplemented with an intravenous drip of dilute thiopental as needed. A laparotomy and hysterotomy were then performed for cannulation of the fetal common carotid artery and the jugular vein. A catheter was also placed in the amniotic cavity and a 4-mm "R" series pulse transit-time ultrasonic flowmeter (Transonic), sensitive enough to detect changes in blood flow of at least 10%, was secured around a branch of the uterine artery supplying the pregnant horn (14). During abdominal closure, all catheters and the flowmeter cable were tunneled subcutaneously and exteriorized within a pouch attached to the ewe's flank. The aorta and superior vena cava were also cannulated through the carotid artery and jugular vein after local infiltration with 2-chloroprocaine. Animals were then allowed to recover for at least 4 days. Antibiotics were administered twice daily to the mother and fetus throughout the recovery and study periods.

On the day of experiment, the ewe was weighed and kept standing in a cart. During a control period of at least 60 min and throughout the study, the maternal and fetal heart rates and arterial blood pressures were continuously recorded on a polygraph. The central venous pressure, intraamniotic pressure, and uterine blood flow, were recorded. The maternal and fetal arterial pH and blood gas tensions were also determined. Only ewes and fetuses in good condition were studied.

At the conclusion of the 45–60-min control period, the ewe was given each of the following five regimens in random order:

a. A 15-min intravenous ropivacaine infusion at a constant rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$, followed by 45 min of infusion at a rate of 0.05 $mg \cdot kg^{-1} \cdot min^{-1}$ (Rop Lo)
b. A 15-min intravenous bupivacaine infusion at a constant rate of 0.077 $mg \cdot kg^{-1} \cdot min^{-1}$ followed by 45 min of infusion at a rate of 0.039 $mg \cdot kg^{-1} \cdot min^{-1}$ (Bup Lo)
c. A 15-min intravenous ropivacaine infusion at a constant rate of 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ followed by 45 min of infusion at a rate of 0.075 $mg \cdot kg^{-1} \cdot min^{-1}$ (Rop Hi)
d. A 15-min intravenous bupivacaine infusion at a constant rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ followed by 45 min of infusion at a rate of 0.058 $mg \cdot kg^{-1} \cdot min^{-1}$ (Bup Hi)
e. A 30-min intravenous infusion of epinephrine at a rate of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Epi)

A 1-day recovery period separated local anesthetic infusions. An interval of 7–8 h was allowed between epinephrine and local anesthetic infusions.

The Rop Lo and Bup Lo infusion rates were selected on the basis of preliminary studies to achieve plasma concentrations of local anesthetic at 60 min that were similar to those occurring during epidural anesthesia in humans (15,16). To ascertain the effects of higher maternal plasma concentrations of these drugs, we attempted to double their infusion rates. Although this was well tolerated with ropivacaine, pilot studies indicated that only a 25% increase in the bupivacaine infusion rate could be tolerated without overt signs of systemic toxicity. Epinephrine, known to constrict uterine arteries in a dose-dependent manner (17), was administered at a rate that in our preliminary studies resulted in a 15%–25% decrease in uterine artery blood flow within 30 min of infusion.

Arterial blood samples were drawn from the mother during the control period, and at 15, 30, 45, and 60 min of local anesthetic infusion. Fetal blood samples were drawn before, and at 15, 30, and 60 min of anesthetic infusion. These were centrifuged, the plasma was separated and frozen at −20°C to be subsequently analyzed for local anesthetic concentrations using a gas chromatographic technique similar to that described by Nancarrow et al. (18). The assay was calibrated to measure concentrations down to 50 ng/mL. Concentrations are reported as micrograms of drug hydrochloride per milliliter of plasma in keeping with the clinical formulation. Throughout the course of the study, the assay coefficients of variation were: bupivacaine, 7% at 1 μg/mL; ropivacaine, 4% at 1 μg/mL. Maternal and fetal arterial blood pH and gas tensions were determined in aliquots of blood obtained before, at 15 min, and at the end of drug infusion. During epinephrine administration, maternal and fetal acid-base status was determined at 0, 15, and 30 min.

Changes in monitored and measured variables were evaluated for statistical significance using analyses of variance for repeated measures (Sheffe F test). A *P* value less than 0.05 was considered to be significant. All results are expressed as mean ± SE.

Results

A total of 39 studies were performed on 10 pregnant ewes, which were similar in weight and gestational age (Table 1). A brief episode of twitching and tremors because of an accidental high rate of infusion developed in one animal receiving a high-dose regimen of ropivacaine. Data regarding this particular study were excluded from analysis. Maternal plasma concentrations of local anesthetics obtained with low- and high-dose infusion regimens are shown in Table 2. At 60 min, these were: Rop Lo, 1.60 ± 0.35; Bup Lo, 1.55 ± 0.15; Rop Hi, 2.50 ± 0.37; and Bup Hi, 1.83 ± 0.19 μg/mL.

All animals were in good condition before each

Table 1. Weight and Gestational Age at Time of Study

	n	Weight (kg)	Gestational age (days)
Rop Lo	7	63.5 ± 3.6	128.3 ± 0.5
Bup Lo	7	64.6 ± 3.5	128.4 ± 0.8
Rop Hi	8	63.0 ± 3.5	128.0 ± 0.8
Bup Hi	8	63.0 ± 3.5	128.1 ± 1.2
Epi	9	64.8 ± 2.9	127.9 ± 0.8

Rop, ropivacaine; Bup, bupivacaine; Epi, epinephrine; Lo, low infusion rate; Hi, high infusion rate.

Values are mean ± SE; differences are not statistically significant.

Table 2. Plasma Concentrations of Local Anesthetics in Ewes and Fetuses

	Plasma concentration (μg/mL)			
Anesthetic	15 min	30 min	45 min	60 min
Ewes				
Rop Lo	1.99 ± 0.38	1.46 ± 0.32	1.49 ± 0.31	1.60 ± 0.35
Bup Lo	1.96 ± 0.15	1.51 ± 0.13	1.50 ± 0.12	1.55 ± 0.15
Rop Hi	3.42 ± 0.43	2.30 ± 0.41	2.44 ± 0.35	2.50 ± 0.37
Bup Hi	1.85 ± 0.21	1.65 ± 0.18	1.65 ± 0.18	1.83 ± 0.19
Fetuses				
Rop Lo	0.21 ± 0.03	0.20 ± 0.03		0.28 ± 0.05
Bup Lo	0.22 ± 0.08	0.22 ± 0.08		0.28 ± 0.09
Rop Hi	0.54 ± 0.05	0.43 ± 0.04		0.57 ± 0.05
Bup Hi	0.26 ± 0.04	0.25 ± 0.03		0.32 ± 0.02

Rop, ropivacaine; Bup, bupivacaine; Epi, epinephrine; Lo, low infusion rate; Hi, high infusion rate.

Values are mean ± SE.

Table 3. Maternal Mean Arterial Blood Pressure, Heart Rate, and Uterine Blood Flow Before, at 15 Minutes, and at the End of Infusion

Variables	Before infusion	15 Min	End of infusion
Rop Lo			
MABP	109 ± 4	114 ± 5	115 ± 5
HR	116 ± 7	105 ± 7[a]	110 ± 6
UBF	436 ± 59	454 ± 50	454 ± 43
Bup Lo			
MABP	102 ± 6	103 ± 5	103 ± 6
HR	113 ± 9	102 ± 10	96 ± 7[a]
UBF	463 ± 58	451 ± 65	456 ± 60
Rop Hi			
MABP	102 ± 4	108 ± 4	103 ± 4
HR	111 ± 8	106 ± 7	105 ± 7
UBF	479 ± 56	433 ± 49	478 ± 48
Bup Hi			
MABP	104 ± 3	113 ± 4	111 ± 2
HR	112 ± 7	103 ± 6	100 ± 7
UBF	441 ± 52	410 ± 55	420 ± 61
Epi			
MABP	113 ± 7	119 ± 6	114 ± 6
HR	111 ± 9	128 ± 7[a]	146 ± 7[a]
UBF	544 ± 34	423 ± 43[a]	408 ± 45[a]

MABP, mean arterial blood pressure; HR, heart rate; UBF, uterine blood flow; Rop, ropivacaine; Bup, bupivacaine; Epi, epinephrine; Lo, low infusion rate; Hi, high infusion rate.

Values are mean ± SE. MABP, in mm Hg; HR, in beats/min; and UBF, in mL/min.

[a] Significantly different from values before infusion.

experiment; heart rate, mean arterial blood pressure, pH, and gas tensions were normal (Tables 3 and 4). Low-dose regimens of both drugs were associated with a small but statistically significant decrease in maternal heart rate from a preinfusion value of 116 ± 7 to 105 ± 7 beats/min at 15 min of Rop Lo and from a control of 113 ± 9 to 96 ± 7 beats/min at 60 min of Bup Lo (Table 3). Although similar trends were noted after high-dose regimens, these decreases in heart rate were not statistically significant. Epinephrine infusion resulted in a significant increase in maternal heart rate from 111 ± 9 to 128 ± 7 beats/min at 15 min and to 146 ± 7 beats/min at 30 min. None of the infusion regimens were associated with significant changes in maternal mean arterial blood pressure. There were also no significant changes in intraamniotic and central venous pressures during any of the studies. Local anesthetics did not alter uterine blood flow at any time, whereas epinephrine infusion resulted in an approximately 25% reduction at 15 and 30 min (end of infusion) (Table 3).

There were few changes in maternal arterial blood pH and gas tensions during administration of local anesthetics (Table 4). With Bup Hi, there was a decrease in carbon dioxide tension (P_{CO_2}) from 34 ± 1 to 29 ± 2 mm Hg, which was accompanied by an increase in arterial pH from 7.49 ± 0.02 to 7.54 ± 0.02 at 15 min of infusion. Both values returned to baseline by the end of the experiment. Epinephrine infusion resulted in a small but significant decrease in maternal P_{CO_2}, whereas the decrease in pH did not reach statistical significance.

Before each study, indices of fetal condition were normal (Tables 5 and 6). Fetal plasma concentrations of local anesthetic at the end of maternal infusion were as follows: Rop Lo ($n = 5$), 0.28 ± 0.05; Bup Lo ($n = 6$), 0.28 ± 0.09; Rop Hi ($n = 6$), 0.57 ± 0.05; and Bup Hi ($n = 8$), 0.32 ± 0.02 μg/mL (Table 2). Owing to technical difficulties, fetal plasma concentrations of local anesthetic at 60 min were not determined in all experiments. The calculated fetal-maternal plasma concentration ratios at 60 min did not differ significantly among groups: Rop Lo, 0.22 ± 0.04; Bup Lo, 0.19 ± 0.05; Rop Hi, 0.28 ± 0.05; Bup Hi, 0.19 ± 0.02.

Fetal heart rate and mean arterial blood pressure were unaffected by maternal infusion of local anesthetic or epinephrine (Table 5). Administration of the lower dose regimens of ropivacaine and bupivacaine to the ewe did not alter fetal arterial blood pH and gas tensions (Table 6). With high-dose infusion regimens of both drugs, there was a small but significant decrease in fetal P_{O_2} from a control of 29 ± 2 to 26 ± 2 mm Hg at 15 min of Rop Hi and from 35 ± 4

Table 4. Maternal Arterial Blood pH and Gas Tensions Before, at 15 Minutes, and at the End of Infusion

Variables	Before infusion	15 Min	End of infusion
Rop Lo			
pH	7.51 ± 0.01	7.52 ± 0.01	7.53 ± 0.01
P_{CO_2}	34 ± 1	31 ± 1	33 ± 1
P_{O_2}	96 ± 2	96 ± 3	96 ± 2
Bup Lo			
pH	7.47 ± 0.03	7.51 ± 0.01	7.50 ± 0.02
P_{CO_2}	33 ± 1	31 ± 1	31 ± 1
P_{O_2}	94 ± 2	97 ± 2	98 ± 1
Rop Hi			
pH	7.51 ± 0.01	7.50 ± 0.01	7.50 ± 0.02
P_{CO_2}	31 ± 1	30 ± 1	33 ± 2
P_{O_2}	97 ± 2	96 ± 2	95 ± 3
Bup Hi			
pH	7.49 ± 0.02	7.54 ± 0.02^a	7.52 ± 0.02
P_{CO_2}	34 ± 1	29 ± 2^a	32 ± 1
P_{O_2}	96 ± 2	94 ± 2	91 ± 2
Epi			
pH	7.50 ± 0.01	7.49 ± 0.01	7.43 ± 0.03
P_{CO_2}	34 ± 1	28 ± 1^a	26 ± 2^a
P_{O_2}	97 ± 2	99 ± 2	93 ± 4

P_{CO_2}, carbon dioxide tension; P_{O_2}, oxygen tension; Rop, ropivacaine; Bup, bupivacaine; Epi, epinephrine; Lo, low infusion rate; Hi, high infusion rate.

Values are mean ± SE. P_{CO_2} and P_{O_2}, in mm Hg.

^{a}Significantly different from values before infusion.

Table 6. Fetal Arterial Blood pH and Gas Tensions Before, at 15 Minutes, and at the End of Infusion

Variables	Before infusion	15 Min	End of infusion
Rop Lo			
pH	7.38 ± 0.02	7.38 ± 0.02	7.38 ± 0.02
P_{CO_2}	38 ± 1	39 ± 2	41 ± 2
P_{O_2}	30 ± 3	29 ± 3	29 ± 3
Bup Lo			
pH	7.38 ± 0.02	7.40 ± 0.02	7.41 ± 0.02
P_{CO_2}	36 ± 2	37 ± 0.05	40 ± 2
P_{O_2}	26 ± 1	26 ± 1	26 ± 1
Rop Hi			
pH	7.38 ± 0.01	7.38 ± 0.01	7.39 ± 0.02
P_{CO_2}	42 ± 2	42 ± 3	41 ± 3
P_{O_2}	29 ± 2	26 ± 2^a	28 ± 2
Bup Hi			
pH	7.41 ± 0.01	7.40 ± 0.02	7.41 ± 0.01
P_{CO_2}	36 ± 1	36 ± 0.04	35 ± 1
P_{O_2}	35 ± 4	32 ± 3	30 ± 2^a
Epi			
pH	7.40 ± 0.01	7.40 ± 0.01	7.38 ± 0.01
P_{CO_2}	35 ± 2	34 ± 2	34 ± 2
P_{O_2}	29 ± 2	31 ± 4	28 ± 2

P_{CO_2}, carbon dioxide tension; P_{O_2}, oxygen tension; Rop, ropivacaine; Bup, bupivacaine; Epi, epinephrine; Lo, low infusion rate; Hi, high infusion rate.

Values are mean ± SE. P_{CO_2} and P_{O_2}, in mm Hg.

^{a}Significantly different from values before infusion.

Table 5. Fetal Mean Arterial Blood Pressure and Heart Rate Before, at 15 Minutes, and at the End of Infusion

Variables	Before infusion	15 Min	End of infusion
Rop Lo			
MABP	44 ± 6	45 ± 7	48 ± 8
HR	163 ± 8	174 ± 10	163 ± 7
Bup Lo			
MABP	51 ± 3	53 ± 2	52 ± 2
HR	182 ± 12	174 ± 9	163 ± 2
Rop Hi			
MABP	49 ± 3	49 ± 4	49 ± 3
HR	153 ± 8	158 ± 7	151 ± 8
Bup Hi			
MABP	49 ± 5	51 ± 5	53 ± 5
HR	156 ± 7	162 ± 7	152 ± 10
Epi			
MABP	43 ± 4	42 ± 4	43 ± 4
HR	165 ± 7	178 ± 10	171 ± 5

MABP, mean arterial blood pressure; HR, heart rate; Rop, ropivacaine; Bup, bupivacaine; Epi, epinephrine; Lo, low infusion rate; Hi, high infusion rate.

Values are mean ± SE. MABP, in mm Hg; HR, in beats/min.

Differences not statistically significant.

to 30 ± 2 mm Hg at 60 min of Bup Hi. There were no significant fetal acid-base changes during maternal epinephrine infusion.

Discussion

These data indicate that intravenous infusions of ropivacaine and bupivacaine, resulting in plasma concentrations relevant to clinical practice (15,16), do not adversely affect the pregnant ewe and her fetus. Even with larger dose regimens, maternal and fetal well-being was well preserved. To achieve similar maternal plasma concentrations of both drugs, the low-infusion regimen of ropivacaine was approximately 25% more than that of bupivacaine. This difference could be a result of a greater clearance of ropivacaine (19). Similarly, in an earlier study, our group found that the ropivacaine doses required to produce seizures were higher in both nonpregnant and pregnant ewes compared with those of bupivacaine, whereas plasma concentrations of both drugs were similar (11). In the present study, doubling the infusion rate of ropivacaine (Rop Hi) was well tolerated, although it resulted in maternal plasma concentrations that were almost twice as high as with Rop Lo. In contrast, the animals could only tolerate a 25% increase in bupivacaine infusion rate without overt signs of systemic toxicity.

Pregnant ewes were in good condition throughout all studies. The small but statistically significant decrease in heart rate during low-dose infusion of either local anesthetic is most likely not drug-related, although there is potential for amide local anesthetics to cause sedation or to have a direct effect on the myocardium and conduction system (8,9). A similar trend in maternal heart rate was also noted with higher dose infusions of either drug, but these changes were not statistically significant. The magnitude of maternal heart rate changes observed in this study were of no consequence, as other determinants of well-being, particularly mean arterial blood pressure and acid-base status, were generally unaffected. Epinephrine administration was associated with significant maternal tachycardia but without an increase in mean arterial blood pressure. This could be attributed to the relatively low dosage of epinephrine used and to the fact that sheep may be resistant to the vasopressor effects of catecholamines (20,21).

The appropriateness of using this animal preparation for the measurement of uterine blood flow was established by infusion of epinephrine that resulted in a 20%-25% reduction. Others have also demonstrated that epinephrine decreases uterine blood flow in pregnant sheep (17). None of the local anesthetic regimens administered adversely affected uterine blood flow. This is particularly reassuring in the case of ropivacaine for two reasons. First, plasma concentrations of the drug achieved with the high-dose infusion regimen were approximately twice as large as those reported in nonpregnant individuals after administration of epidural anesthesia to a midthoracic sensory level (15). Ropivacaine has not yet been used for epidural anesthesia during parturition. Second, ropivacaine is a vasoconstrictor (12). However, a recent abstract by the same group suggests that neither ropivacaine nor bupivacaine reduces capillary blood flow (22). The present study demonstrates that neither drug decreased uterine blood flow in pregnant sheep. However, a potential limitation of measuring uterine artery blood flow alone is that it does not provide data on relative placental and nonplacental perfusion (23). An increase in uterine tone, which in itself may reduce uterine blood flow (1), was not observed in any of our experiments.

A decrease in uterine blood flow owing to uterine artery vasoconstriction and myometrial stimulation occurred in pregnant ewes given intraaortic infusions of several amide local anesthetics (1). However, drug levels in the uterine vasculature were much higher than would normally be expected to occur during clinical obstetric anesthesia. Indeed, in another study involving pregnant ewes, uterine blood flow and intraamniotic pressure were not affected when lidocaine was infused to achieve maternal arterial blood concentrations of 0.81-4.6 μg/mL (24). As maternal convulsions may be associated with decreased uterine blood flow, infusion regimens in the present study were chosen so as not to result in central nervous system toxicity.

It is not surprising that there is little difference in the steady-state feto-maternal plasma concentration ratios of ropivacaine and bupivacaine considering the physicochemical similarities between them (11,25). The plasma concentrations of both local anesthetics achieved in the fetus were not associated with a deterioration in the commonly measured indices of well-being. Neither did the epinephrine infusion have an adverse effect on the fetus, possibly because a well fetus can tolerate a reduction in uterine blood flow not exceeding 25% (26). The reason for the small but significant decrease in fetal Po_2 seen with higher infusion regimens of either drug is unclear and probably of no consequence. It could be related, in part, to umbilical cord vasoconstriction shown to occur in vitro with higher concentrations of amide local anesthetics such as bupivacaine (27).

In conclusion, neither ropivacaine nor bupivacaine, as administered in this study, led to any ill effects on the pregnant ewe and her fetus.

References

1. Greiss FC, Still JG, Anderson SG. Effects of local anesthetic agents on the uterine vasculatures and myometrium. Am J Obstet Gynecol 1976;124:889-99.
2. Gibbs CP, Noel SC. Human artery responses to lidocaine. Am J Obstet Gynecol 1976;126:313-5.
3. Cibils LA. Response of human arteries to local anesthetics. Am J Obstet Gynecol 1976;126:202-10.
4. Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. Br J Anaesth 1991;66:31-7.
5. Akerman B, Hellberg IB, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 1988;32:571-8.
6. Feldman HS, Arthur GR, Covino BG. Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine and lidocaine in the conscious dog. Anesth Analg 1989;69:794-801.
7. Reiz S, Haggmark G, Johansson G, Nath S. Cardiotoxicity of ropivacaine—a new amide local anaesthetic agent. Acta Anaesthesiol Scand 1989;33:93-8.
8. Arlock P. Actions of three local anaesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (V max). Pharmacol Toxicol 1988;63:96-104.
9. Moller R, Covino BG. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared to those of ropivacaine, a new amide local anesthetic. Anesthesiology 1990;72:322-9.
10. Morishima HO, Pedersen H, Finster M, et al. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63:134-9.
11. Santos AC, Arthur GR, Pedersen H, Morishima HO, Finster M, Covino BG. Systemic toxicity of ropivacaine during ovine pregnancy. Anesthesiology 1991;75:137-41.
12. Kopacz DJ, Carpenter RL, Mackey DC. Effect of ropivacaine on cutaneous capillary blood flow in pigs. Anesthesiology 1989; 71:69-74.
13. Santos AC, Pedersen H, Sallusto JA, et al. Pharmacokinetics of ropivacaine in nonpregnant and pregnant ewes. Anesth Analg 1990;70:262-6.
14. Burton RG, Gorewit RC. Ultrasonic flowmeter uses wide-beam transit-time technique. Med Electron Data 1984;15:68-73.
15. Concepcion M, Arthur GR, Steele SM, Bader AM, Covino BG. A new local anesthetic, ropivacaine: its epidural effects in humans. Anesth Analg 1990;70:80-5.
16. Pihlajamki K, Kanto J, Lindberg R, Karanko M, Kiilholma P. Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women. Br J Anaesth 1990;64:556-62.

17. Greiss FC. The uterine vascular bed: effect of adrenergic stimulation. Obstet Gynecol 1963;21:295–301.
18. Nancarrow C, Runciman WB, Mather LE, Upton RN, Plummer JL. The influence of acidosis on the distribution of lidocaine and bupivacaine into the myocardium and brain of sheep. Anesth Analg 1987;66:925–33.
19. Arthur GR, Feldman HS, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. Anesth Analg 1988;67:1053–8.
20. Fishburne JI, Meis PJ, Urban RB, et al. Vascular and uterine responses to dobutamine and dopamine in the gravid ewe. Am J Obstet Gynecol 1980;137:944–52.
21. Fishburne JI, Dormer KJ, Payne GG, et al. Effects of amrinone and dopamine on uterine blood flow and vascular responses in the gravid baboon. Am J Obstet Gynecol 1988;158:829–37.
22. Guinard JP, Carpenter RL, Owens BD, Nadir B. Does ropivacaine induce vasoconstriction? Anesthesiology 1990;73:A847.
23. Greiss FC. Differential reactivity of the myoendometrial and placental vasculature: vasodilation. Am J Obstet Gynecol 1971; 111:611–25.
24. Biehl D, Shnider SM, Levinson G, Callender K. The direct effects of circulating lidocaine on uterine blood flow and foetal well-being in the pregnant ewe. Can Anaesth Soc J 1977;24: 445–51.
25. Strichartz GR, Sanchez V, Arthur GR, Chafez R, Martin D. Fundamental properties of local anesthetics. II. Measured octanol: buffer partition coefficient and pK_a values of clinically used drugs. Anesth Analg 1990;71:158–70.
26. Greiss FC. Uterine blood flow during pregnancy. Med Coll VA Q 1972;8:52–60.
27. Halevy S, Monuszko E, Freese KJ, Altura BM. Local anesthetics interaction with hypoxia, hypercarbia-induced acidosis and histamine on umbilical vascular reactivity. Anesthesiology 1988;69:A673.

Attenuation of Gastric Effects of Famotidine by Preoperative Administration of Intravenous Fluids

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Effects of preoperative administration of intravenous crystalloids on the gastric effects of famotidine were studied in 89 patients scheduled for elective surgery in the afternoon. Patients were randomly assigned to one of six groups. Groups P1, P2, and P3 received 2.0 mL of intramuscular saline (placebo) and groups F1, F2, and F3 received 20 mg of intramuscular famotidine 1 h before anesthesia. All patients fasted for 14–18 h before surgery. No fluid was administered to groups P1 and F1 preoperatively, whereas 500 mL of intravenous fluid was given to the other groups over a period of 4–5 h before anesthesia: a maintenance fluid with 10% glucose to groups P2 and F2, and lactated Ringer's solution without glucose to groups P3 and F3. After anesthetic induction, the stomach was aspirated using a nasogastric tube and volume and pH of the contents were measured. The gastric volume was significantly less in F2 (4.2 ± 1.2 mL, mean ± SEM) than in P1 (30.7 ± 5.5 mL) ($P < 0.01$) and in F3 (12.7 ± 2.1 mL) than in P3 (26.8 ± 4.4 mL) ($P < 0.05$). There was no significant difference between P2 (23.4 ± 4.6 mL) and F2 (17.5 ± 3.5 mL). Mean pH values were significantly higher in F1 (6.82 ± 0.48) than in P1 (3.21 ± 0.72) ($P < 0.01$). No significance was observed between P2 (3.65 ± 0.62) and F2 (4.53 ± 0.77), or P3 (3.17 ± 0.81) and F3 (5.03 ± 0.80). Further, there was a significant difference within famotidine groups (F1 vs F2 and F3) with respect to volume ($P < 0.01$) and pH ($P < 0.05$) but no difference within placebo groups. The intravenous fluid with 10% glucose does not alter gastric secretion. The results indicate that the ability of famotidine to reduce the volume of gastric contents and increase its pH is attenuated by preoperative administration of intravenous fluids. Yet, preoperative administration of fluids had no influence on the number of patients "at risk" (gastric volume > 25 mL and pH < 2.5) for aspiration of gastric contents.

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Since the first description of pulmonary aspiration of gastric contents by Mendelson in 1946 (1), this potentially fatal perioperative complication remains a major threat to patient morbidity and mortality. The severity of subsequent pulmonary damage is related to gastric volume and its pH, and an aspirated fluid volume of >25 mL at pH < 2.5 has been proposed as a risk factor of severe pulmonary damage (2). For prophylaxis against this type of pulmonary complication, preoperative overnight fasting for more than 8 h is often combined with the use of a histamine H_2 antagonist such as cimetidine (3), ranitidine (4), or famotidine (5,6), of which famotidine is the most potent with the longest duration of action (7). Yet, fasting for more than 12 h is imposed on patients undergoing operations in the afternoon, causing dehydration that may lead to intravascular hypovolemia with intraoperative oliguria or circulatory instability (8). Preoperative intravenous fluid therapy is a reasonable precaution against these complications. However, it has been our clinical impression that the volume of gastric fluid aspirated through a gastric tube after induction of anesthesia is larger in patients hydrated with preoperative intravenous fluid than in dehydrated patients, irrespective of preoperative administration of famotidine. The present study was conducted to clarify the effects of preoperative intravenous fluids on the gastric inhibitory effects of famotidine.

Methods

The protocol was approved by the ethical committee of our institute, and written consent was obtained from all patients. Eighty-nine patients aged 17–59 yr (mean 42.2 yr) undergoing gynecologic, orthopedic, or ear, nose, and throat surgery under general anesthesia in the afternoon were studied. Patients with a history of gastrointestinal disease or severe systemic disease were excluded. All patients fasted from mid-

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Table 1. Patient Groups

Group	n	H_2-antagonist	IV fluid
P1	16	Placebo	—
P2	15	Placebo	Physiosol-3 (500 mL)
P3	15	Placebo	Lactated Ringer's solution (500 mL)
F1	18	Famotidine (20 mg)	—
F2	13	Famotidine (20 mg)	Physiosol-3 (500 mL)
F3	12	Famotidine (20 mg)	Lactated Ringer's solution (500 mL)

IV, intravenous.

Table 2. Patient Characteristics

Group	M/F	Age (yr)	Weight (kg)	Duration of fast (h)
P1	6:10	44.3 ± 1.1	54.8 ± 1.6	17.5
P2	7:8	44.9 ± 1.3	53.9 ± 2.4	16.4
P3	6:9	39.5 ± 2.5	54.2 ± 1.6	17.3
F1	9:9	41.8 ± 2.5	56.4 ± 1.9	17.1
F2	5:8	42.7 ± 1.8	55.8 ± 2.1	16.5
F3	5:7	39.5 ± 2.8	55.1 ± 2.1	17.6
P	NS	NS	NS	NS

NS, there were no significant differences among the six groups.
Values are mean ± SEM.

Table 3. Gastric Content Volume and pH

	Premedication		
Group	Placebo	Famotidine	P/F
Gastric volume			
P1 vs F1	30.7 ± 5.5	4.2 ± 1.2[a,b]	7.31
P2 vs F2	23.4 ± 4.6	17.5 ± 3.5	1.34
P3 vs F3	26.8 ± 4.4	12.7 ± 2.1[c]	2.11
	$P > 0.05$	$P < 0.01$	
Gastric pH			
P1 vs F1	3.21 ± 0.72	6.82 ± 0.48[a,d]	
P2 vs F2	3.65 ± 0.62	4.53 ± 0.77	
P3 vs F3	3.17 ± 0.81	5.03 ± 0.80	
	$P > 0.05$	$P > 0.05$	

Values are mean ± SEM.
[a] $P < 0.01$ vs placebo.
[b] $P < 0.01$ vs F2 + F3.
[c] $P < 0.05$ vs placebo.
[d] $P < 0.05$ vs F2 + F3.

night until surgery and were randomly assigned to one of six groups for preoperative medications and intravenous fluids (Table 1). Preoperative medication, administered intramuscularly 1 h before anesthetic induction, was 2 mL of saline (placebo) for groups P1–P3 or 20 mg of famotidine in 2 mL of saline for groups F1–F3. Simultaneous intramuscular atropine, 0.5 mg, was administered to reduce salivary secretion. Although anticholinergics have some gastric effects by reducing lower esophageal sphincter pressure (9) or by reducing gastric secretion (10), atropine given in clinical regimens does not change gastric volume and acidity (10,11). Fluids, 500 mL IV, were infused over a period of 4–5 h before anesthetic induction, except for the P1 and F1 groups, which received no fluid. Physiosol-3 (Green Cross Corporation, Osaka, Japan), a maintenance fluid containing 10% glucose, was administered to groups P2 and F2, and lactated Ringer's solution to groups P3 and F3. General anesthesia was induced with intravenous thiopental and succinylcholine.

Aspiration of gastric contents was performed by an investigator, who was not involved in the anesthetic procedure and was unaware as to which group the patient had been assigned. After tracheal intubation, a nasogastric Salem sump-tube (14F, Argyle) was inserted and its position was verified by auscultation of injected air through the tube. In an attempt to empty the stomach as completely as possible, aspiration was performed through the tube using a 50-mL syringe, locating the tube tip at several points within the stomach. The volume of aspirate in the syringe was measured and its pH was determined using Hydrogen Ion Concentration Test Paper (Toyo Roshi, Tokyo, Japan).

Twelve patients, seven from group F1 and five from group F2, were selected randomly for comparison of their urinary osmolality. Urine obtained from the urethral catheter just after anesthetic induction was sampled, and its osmolality was measured using an Osmometer OM801 (Vogel, Giessen, Germany).

Results were expressed as mean ± SEM. Data were analyzed using the Kruskal-Wallis test or Mann-Whitney U-test. Patients with a gastric volume of >25 mL and pH of <2.5 were defined as being "at risk" of severe pulmonary complication. Either χ^2 analysis or Fisher's exact probability analysis was used to compare the proportions of patients at risk in the six groups. Differences were considered statistically significant when P values were less than 0.05.

Results

There were no significant differences among the six groups with regard to sex, age, weight, and duration of fasting (Table 2). Anesthesia was induced between 1 and 3 PM. Patients fasted for 14–18 h (mean 16.4 h) before surgery.

Effects of famotidine on the volume and pH of gastric contents are summarized in Table 3. Compared with the placebo groups, the famotidine groups had a lower gastric volume and acidity, although statistical significance was not demonstrated for all comparisons. Effects of famotidine on gastric

Table 4. Incidence of Risk Factors for Pulmonary Complication[a]

Without famotidine		With famotidine	
Group	Patients at risk	Group	Patients at risk
P1	7/16[b]	F1	0/18
P2	2/15	F2	2/13
P3	6/15[c]	F3	1/12
P	NS	*P*	NS

NS, there were no significant differences among groups P1–P3 or among groups F1–F3.

[a] Volume >25 mL and pH <2.5.

[b] $P < 0.01$ vs group F1.

[c] $P < 0.05$ vs group F3.

volume for each fluid regimen were also compared. Famotidine markedly decreased the gastric volume in group F1, who did not receive preoperative fluid, as shown by a high P:F ratio (Table 3). However, its effects were less evident in groups F2 and F3 with a low P:F ratio. The gastric inhibitory effects of famotidine were reduced in groups given intravenous fluids. Similarly, the effects of famotidine on gastric pH were less evident in groups F2 and F3 than in group F1.

The proportion of patients at risk was significantly lower in group F1 than in group P1, and in group F3 than in P3 (Table 4), indicating a smaller risk for patients given famotidine. Among the famotidine groups, no patient with risk factors was found in group F1, whereas one or two patients at risk were found in the hydrated groups.

Among placebo groups P1–P3, the fluid regimens did not alter gastric volume or pH. However, the other three groups F1–F3 differed significantly with respect to both volume and pH, demonstrating increased volume and acidity with administration of intravenous fluids preoperatively.

Mean urine osmolality of dehydrated patients was 832 ± 14.7 mOsm/kg ($n = 7$) and that of hydrated patients 592 ± 35.2 mOsm/kg ($n = 5$); the difference was significant ($P < 0.05$).

Discussion

Many studies have demonstrated beneficial effects of preoperative administration of histamine H_2 antagonists in reducing gastric volume and acidity, which was also demonstrated by our study. Some previous studies have evaluated the effects of various drugs in patient groups controlled for various preoperative conditions including age (12), preoperative oral fluid administration (13–15), or combined preoperative medications (16). However, influence of preoperative administration of intravenous fluids has not been determined. We demonstrated that the gastric effects of famotidine were attenuated when intravenous fluids were administered preoperatively, suggesting that dehydration after preoperative fasting and rehydration with intravenous fluid alter the gastric effects of famotidine.

Price and Lauener (17) demonstrated in humans that water restriction for a period of 8 h was sufficient to increase urine osmolality to 793 mOsm/kg, and that oral intake of 20 mL/kg of water returned the urine osmolality to 71 mOsm/kg, reflecting suppressed vasopressin secretion. In our study, the patients without preoperative administration of intravenous fluids had been dehydrated for a period of 14–18 h, and urine osmolality in the patients without preoperative administration of fluids was appreciably more than that in patients given intravenous fluids. Compared with the data in the study of Price and Lauener, duration of water restriction in P1 and F1 patients was apparently long enough to induce dehydration to a significant extent, and rehydration with 500 mL of intravenous fluid was effective for the recovery from dehydration.

Dehydration can influence the effects of famotidine by altering its pharmacokinetics. As famotidine is mainly excreted from the kidney (7), changes in blood flow to the kidney during dehydration could modulate the pharmacokinetics of famotidine. Although little information is available concerning organ blood flow during dehydration in humans, Liard et al. (18) found in dogs that water deprivation for 48 h or vasopressin infusion without dehydration preserved renal and splanchnic blood flow, whereas it markedly decreased the flow of blood to muscles. If this occurred in humans, the effect of dehydration on the pharmacokinetics of famotidine would involve a change in drug distribution rather than a change in drug elimination by the kidney or liver. Reduced blood flow to muscles can limit the second phase of drug distribution, during which a drug in highly perfused organs is delivered to muscles and other organs, resulting in a sustained level of the drug in target organ tissues. Thus, under these circumstances, augmented effects of famotidine on gastric secretion during dehydration can be assumed. Conversely, rehydration should attenuate the effects of famotidine by increasing the flow of blood to muscles.

We used standards, i.e., gastric volume of >25 mL with a pH of <2.5, for identifying patients at risk of severe pulmonary complication. Although its validity has not been well established, it is the standard by which various physiologic and pharmacologic maneuvers are evaluated. The proportion of the patients at risk was not changed by administration of preoperative intravenous fluid. Although intravenous fluid increased gastric volume and acidity in famotidine groups, few of these changes exceeded the level of the standards for risk. However, it should not mean that preoperative intravenous fluids add no risks for aspiration of gastric contents. It is possible that a larger volume of preoperative intravenous fluids revealed an increased risk, as the dosage in our study was rather small for replacement of preoperative body fluid deficit. In addition, the number of patients included in our study seems too small to confirm significant differences among groups concerning the proportion of patients at risk.

A high blood glucose level during intravenous glucose infusion (150 g in 3000 mL of saline) suppresses gastric acid secretion (19). In our study, preoperatively administered glucose dissolved in Physiosol-3 (50 g in 500 mL) did not produce any difference in gastric contents compared with the group given lactated Ringer's solution. However, our result does not necessarily disagree with the latter study, because the amount of glucose given was smaller and elevated blood glucose levels were not confirmed.

In conclusion, we have demonstrated that inhibition of gastric secretion by famotidine is attenuated by preoperative administration of intravenous fluids. Although preoperative intravenous fluids are beneficial for treating dehydration from preoperative fasting, it may also have disadvantages in patients given famotidine. In view of the necessity to minimize the risk of aspiration of gastric contents and development of severe pulmonary complications during anesthesia, the possible risk of preoperative intravenous fluids should be considered.

References

1. Mendelson CL. Aspiration of stomach content into the lung during obstetric anesthesia. Am J Obstet Gynecol 1946;53:191–205.
2. Robert RB, Shirley MA. Reducing the risk of acid aspiration during caesarean section. Anesth Analg 1974;53:859–68.
3. Keating PJ, Black JF, Watson DW. Effects of glycopyrrolate and cimetidine on gastric volume and acidity in patients awaiting surgery. Br J Anaesth 1978;50:1247–9.
4. Francis RN, Kwik RSH. Oral ranitidine for prophylaxis against Mendelson's syndrome. Anesth Analg 1982;61:130–2.
5. Abe K, Shibata M, Demizu A, et al. Effect of oral and intramuscular famotidine on pH and volume of gastric contents. Anesth Analg 1989;68:541–4.
6. Noguchi J, Yamamura H, Inada Y, et al. A double-blind evaluation of famotidine for pre-anesthetic intramuscular administration. Its effects on volume and pH of gastric juice. Masui 1987;36:592–603.
7. Ostro MJ. Pharmacodynamics and pharmacokinetics of parenteral histamine (H_2)-receptor antagonists. Am J Med 1987; 83(Suppl 6A):15–22.
8. Tonnesen AS. Crystalloids and colloids. In: Miller RD, eds. Anesthesia. Edinburgh: Churchill Livingstone, 1990:1439–65.
9. Cotton DR, Smith G. The lower oesophageal sphincter and anaesthesia. Br J Anaesth 1984;56:37–46.
10. Baraka A, Saab M, Salem MR, Winnie AP. Control of gastric acidity by glycopyrrolate premedication in the parturient. Anesth Analg 1977;56:642–5.
11. Salem MR, Wong AY, Mani M, Bennett EJ, Toyama T. Premedicant drugs and gastric juice pH and volume in pediatric patients. Anesthesiology 1976;44:216–9.
12. Noguchi J, Konishi M, Takeda J. Influence of intramuscular famotidine on gastric fluid at anesthetic induction. Kiso To Rinshou (in Japanese) 1986;20:671–5.
13. Hutchinson A, Maltby JR, Reid CRG. Gastric fluid volume and pH in elective inpatients. Part I: coffee or orange juice versus overnight fast. Can J Anaesth 1988;35:12–5.
14. Maltby JR, Reid CRG, Hutchinson A. Gastric fluid volume and pH in elective inpatients. Part II: coffee or orange juice with ranitidine. Can J Anaesth 1988;35:16–9.
15. Sandhar BK, Goresky GV, Maltby JR, Shaffer EA. Effect of oral liquids and ranitidine on gastric fluid volume and pH in children undergoing outpatient surgery. Anesthesiology 1989; 71:327–30.
16. Manchikanti L, Colliver JA, Marrero TC, Roush JR. Ranitidine and metoclopramide for prophylaxis of aspiration pneumonitis in elective surgery. Anesth Analg 1984;63:903–10.
17. Price JDE, Lauener RW. Serum and urine osmolalities in the differential diagnosis of polyuric states. J Clin Endocrinol 1966;26:143–8.
18. Liard JF, Deriaz O, Schelling P, Thibonnier M. Cardiac output distribution during vasopressin infusion or dehydration in conscious dogs. Am J Physiol 1983;243(Heart Circ Physiol 12):H663–H669.
19. Moore JG. Gastric acid suppression by intravenous glucose solution. Gastroenterology 1973;64:434–41.

Cardiovascular Function During Induced Hypotension by Fenoldopam or Sodium Nitroprusside in Anesthetized Dogs

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Fenoldopam, a selective dopamine$_1$ receptor agonist, has been recommended for induced hypotension because it effectively lowers arterial blood pressure and improves renal perfusion. We examined cardiovascular functions during hypotension induced by fenoldopam or sodium nitroprusside. In eight halothane-anesthetized dogs, the left ventricle (LV) was instrumented with pressure and ultrasonic dimension transducers for the assessment of LV contractility using the analysis of the pressure-diameter relationship. Blood flow distribution was measured by radioactive microspheres. Doses of fenoldopam and nitroprusside were titrated to reduce mean arterial blood pressure to 60 mm Hg. After 40 min of hypotension, fenoldopam and nitroprusside caused similar increases in heart rate (17% ± 4% vs 19% ± 10%, respectively) and decreases in systemic vascular resistance (−24% ± 5% vs −27% ± 4%). Hypotension induced by fenoldopam was associated with higher LV end-diastolic pressure (4.4 ± 0.6 vs 2.5 ± 1.1 mm Hg) and end-systolic meridional wall stress (33.0 ± 4.3 vs 17.8 ± 2.1 g/cm^2) when compared with nitroprusside. There were no significant changes in cardiac output and cardiac contractility as expressed by the slope (E_{es}) of the LV end-systolic pressure-diameter relationship, velocity of shortening of the diameter, and percentage of wall thickening of the LV. In contrast to nitroprusside, which decreased renal blood flow from 197 ± 19 to 163 ± 15 mL/min, renal blood flow increased during fenoldopam-induced hypotension from 187 ± 20 to 239 ± 18 mL/min. The increase in renal perfusion was similar in upper, middle, and lower regions of the kidney; however, it was more in the medulla compared with the cortex (37% ± 17% vs 25% ± 7%). Both fenoldopam and nitroprusside decreased splenic blood flow, but neither altered flow to the brain, skin, or myocardium. Muscle and hepatic arterial blood flow were significantly less with fenoldopam than with nitroprusside. Fenoldopam was associated with significantly larger increases in plasma renin activity compared with nitroprusside. The results of this study show an increase in renal blood flow during fenoldopam infusion that may be of advantage particularly when renal hypoperfusion should be avoided.

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Induced hypotension is used to reduce intraoperative blood loss and to improve the surgical field (1). When arterial blood pressure decreases below a critical level, normal perfusion to vital organs is no longer maintained, particularly when vascular autoregulatory mechanisms are attenuated by anesthetics. Therefore, there is a continuing search for a hypotensive agent that can effectively lower arterial blood pressure while preserving blood flow to vital organs.

Recently fenoldopam has been proposed for induced hypotension (2) because of its ability to decrease arterial blood pressure and to enhance renal perfusion and function (3–5). Vasodilation induced by fenoldopam is mediated by activation of the dopamine$_1$ (DA$_1$) receptor, a subtype of the dopaminergic receptors (6). The presence of these receptors in the cerebral, coronary, mesenteric, and other vascular beds suggests that vasodilation may not be limited to the kidney; however, supporting data are lacking.

The present study was designed to test the hypothesis that, during significant reduction in arterial blood pressure, perfusion to the heart, brain, kidney, and mesentery is maintained or possibly increased with fenoldopam. We evaluated fenoldopam as a hypotensive agent by comparing the effects of equipotent doses of fenoldopam and nitroprusside on cardiac performance and output distribution in dogs during halothane anesthesia.

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Methods

Experimental Preparation

Eight adult mongrel dogs of either sex (21–26 kg) were anesthetized with intravenous thiamylal (15 mg/kg); anesthesia was maintained with inhaled 1.5% halothane in oxygen after tracheal intubation. Halothane concentration was measured at end-expiration by mass spectrometry (AIMT, St. Louis, Mo.). Ventilation was controlled using a Harvard respirator to maintain normal arterial blood gas tensions. A semirigid catheter was inserted into the abdominal aorta through a femoral artery for aortic pressure measurement and reference blood sampling. Blood pressure was measured using a Statham pressure transducer (model 23dB, Hato Rey, Puerto Rico). Cardiac output was measured by thermodilution using a pulmonary arterial catheter and an Edwards computer (model COM-1, Santa Ana, Calif.) with 5 mL of iced saline as the indicator. Values of cardiac output were averaged from triplicate measurements.

Through a left thoracotomy in the fifth intercostal space, the pericardium was opened and a flexible polyethylene catheter was inserted into the left atrium through the appendage for microsphere injection. A solid-state Kõnigsberg transducer (model P7, Pasadena, Calif.) was placed in the left ventricular (LV) cavity through a stab wound in the apex for measurements of LV pressure and LV end-diastolic pressure. The Kõnigsberg transducer was calibrated in vitro against a mercury manometer and in vivo against systolic arterial and left atrial pressures. Ultrasonic dimension crystals were implanted in pairs to measure the wall thickness of the LV freewall and the anterior-posterior transverse diameter of the left ventricle. Proper alignment of the crystals was confirmed with a high-frequency Tektronix oscilloscope (model RM647, Beaverton, Ore.). Ventricular dimensions were monitored with a Triton sonomicrometer (model 120, San Diego, Calif.). Electrical drift in the measurement system was minimized by frequent calibration during the experiment. Vascular occluders were placed around both venae cavae for varying preload during assessment of LV contractility. An electromagnetic flow probe was placed around the artery of the left kidney and connected to a Zepeda flowmeter (model SWF-5RD, Seattle, Wash.) for continuous measurement of renal blood flow (RBF).

Regional blood flow was measured using radioactive microspheres as previously described (7). Radioactive microspheres (3M, St. Paul, Minn.) 15 μm in diameter and labeled with ^{141}Ce, ^{85}Sr, ^{95}Nb, or ^{46}Sc were suspended in 10% Dextran in saline containing 0.01% Tween 80. Before injection, the microsphere suspension was ultrasonically and mechanically agitated to achieve complete dispersion. The lack of aggregation of microspheres was verified by microscopic examination. The suspending solution was tested to confirm the absence of any adverse effect on cardiovascular function. Approximately 2–3 million microspheres were injected into the left atrium over 20 s and the injection catheter was flushed with warm normal saline. A reference blood sample was withdrawn from an arterial catheter starting 15 s before the microsphere injection to ensure steady sampling rate and continuing for 2 min at a constant rate of 7.75 mL/min. At the end of the experiment, the animal was killed with halothane overdose and intravenous injection of saturated KCl. The sampled organs were then removed, sectioned, weighed, and counted for radioactivity. Regional blood flow was calculated from the ratio of radioactive count of measured sample over that of reference blood sample and expressed in milliliters per minute per 100 g.

Data Analysis

The data were recorded on a direct writing Gould oscillograph (model 2800S, Cleveland, Ohio) and on magnetic tape (Kyowa, model RTP-600B, Tokyo, Japan). Physiologic signals were digitized at 5-ms intervals using a Techmar 12-bit analog-to-digital converter and stored on floppy disks. Data were analyzed using a modified Asyst program (Asyst, Rochester, N.Y.) and an 80386 microprocessor. Variable parameters, including mean arterial blood pressure, stroke volume, and systemic vascular resistance were calculated using standard formulas. Percent of systolic shortening was calculated as the ratio of systolic dimension change to diastolic dimension. Velocity of shortening of the LV diameter was derived from the diameter signal using a differentiator. Calibration of the differentiator was made by substituting a triangular wave for the diameter signal. Left ventricular end-systolic meridional wall stress was calculated as described by Colan et al. (8):

$$\sigma_{es} = \frac{1.35\,(P_{es})\,(D_{es})}{4\,(h_{es})\,[1 + (h_{es}/D_{es})]},$$

where σ_{es} is the LV end-systolic wall stress in grams per square centimeter, and P_{es}, D_{es}, and h_{es} are LV pressure, internal diameter, and wall thickness at end-systole, respectively.

Cardiac contractility was assessed using the slope E_{es} of the linear regression of the LV end-systolic pressure-diameter relation. Ten to fifteen consecutive heart beats during vena caval occlusion were analyzed at end-systole. The respirator was turned off momentarily during contractility assessment to eliminate respiratory influence on hemodynamic measurements. Ectopic beats and heart beats with RR intervals varying more than 10% during vena caval occlusion were excluded from analysis. Analysis of each cardiac cycle was performed by computer gating. End-systole was defined as the time at which the LV pressure/diameter ratio was maximal and end-diastole as the initial increase in the positive LV dP/dt. The LV pressure-diameter data were fit to the following equation: $P_{es} = E_{es} (D_{es} - D_o)$, where P_{es} and D_{es} are LV end-systolic pressure and diameter respectively, D_o is the intercept of the diameter axis, and E_{es} is the slope. This slope has been reported to be independent of loading conditions and closely related to cardiac inotropy (9–11).

Experimental Protocol

The end-tidal halothane concentration was reduced to 1.0% after completion of the surgical preparation. Experiments were conducted after cardiovascular stability and normal arterial blood gas tensions were observed for 30 min. After a baseline recording, either nitroprusside or fenoldopam was infused using a variable-speed Harvard pump. The infusion dose was titrated to decrease mean arterial blood pressure to 60 mm Hg and recording was made after 40 min of infusion. The drug infusion was then stopped and a 60-min period was allowed for recovery. After a second baseline recording, the second drug was infused to produce an equivalent hypotension and recording was repeated as above. Microspheres were injected at baselines and at 40 min of the nitroprusside and fenoldopam infusions. The sequence of radioactive isotopes and the order of drugs were alternated randomly so each dog served as its own control. Blood samples were collected before microsphere injections and analyzed for plasma renin activity using radioimmunoassay (GAMMACOAT [$^{-125}$I] Plasma Renin Activity Radioimmunoassay Kit).

Data from eight dogs were analyzed using BMDP software and summarized as mean ± SEM. Statistical analysis of data included analysis of variance for repeated measures followed by *t*-test with Bonferroni modification. Probability values less than 0.05 were considered statistically significant.

This study was approved by our institutional committee on the care and use of laboratory animals. The use of animals followed the guidelines of "Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Council (DHHS publication No [NIH] 85-23, 1985).

Results

Hypotension induced by either fenoldopam or nitroprusside was similar in onset and recovery times. Steady-state arterial blood pressure was obtained 3.6 ± 0.8 min after the start of fenoldopam infusion compared with 5.0 ± 0.9 min with nitroprusside. Arterial blood pressure returned to preinfusion level 11.5 ± 2.5 min with fenoldopam vs. 13.3 ± 2.8 min with nitroprusside after termination of infusion. From similar baseline mean arterial blood pressures, the dosages of fenoldopam and nitroprusside required to decrease mean arterial blood pressure to 60 mm Hg were 4.5 ± 1.8 and 4.0 ± 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. In two of the eight dogs, large fenoldopam doses were required to maintain hypotension leading to the reported large standard error of the averaged dose of fenoldopam.

Hemodynamic data obtained at baseline and during hypotension are summarized in Table 1. There were no significant differences between the two baselines. After 40 min of hypotension with either drug, heart rate increased by 17%, whereas systemic vascular resistance decreased by 24%. No significant changes in cardiac output and stroke volume were observed; however, LV end-diastolic pressure showed a greater decrease ($P < 0.05$) during nitroprusside (−52%) than during fenoldopam (−15%) infusion as shown in Figure 1. Renal blood flow decreased slightly but significantly with nitroprusside. This decrease in RBF was not accompanied by a significant change in renal vascular resistance. In contrast, fenoldopam increased RBF by 28% concomitant with a 50% decrease in renal vascular resistance. Neither hypotensive agent altered cardiac contractility assessed by either the slope (E_{es}) of the LV end-systolic pressure-diameter relationship or percent systolic wall thickening or LV diameter shortening velocity. Left ventricular end-systolic meridional wall stress (WS) was reduced to one-half with nitroprusside; in contrast, changes in WS due to fenoldopam were not significantly different from baseline values (Figure 2). Plasma renin activity (PRA) increased during hypotension with both drugs, but the increase in PRA was significantly greater ($P < 0.05$) during fenoldopam infusion. Except for a decrease in Po_2 associated with nitroprusside infusion, blood gas tensions remained unchanged from baseline (Table 1).

Table 2 contains values of organ blood flows measured using radioactive microspheres at baseline and during infusion of either fenoldopam or nitroprusside. There were no significant differences between the two baselines. The transmural blood flow distribution across the LV wall did not change significantly with either agent as shown by the endocardial/epicardial flow ratio. On the contrary, the ratio of

Table 1. Effects of Nitroprusside and Fenoldopam on Baseline Hemodynamics

	Baseline	Nitroprusside	Baseline	Fenoldopam
HR (beats/min)	108 ± 8	126 ± 9^a	107 ± 8	124 ± 8^a
LVP (mm Hg)	110 ± 7	79 ± 4^a	108 ± 5	89 ± 4^a
MAP (mm Hg)	82 ± 5	59 ± 4^a	82 ± 4	61 ± 5^a
LVEDP (mm Hg)	6.6 ± 0.5	2.5 ± 1.1^a	6.7 ± 0.6	4.4 ± 0.6^{a,b}
CO (L/min)	2.61 ± 0.18	2.39 ± 0.22	2.67 ± 0.19	2.76 ± 0.25
SV (mL)	26 ± 3	20 ± 2	26 ± 3	24 ± 3
SVR (mm Hg·L^{-1}·min^{-1})	31.9 ± 2.0	23.1 ± 1.6^a	31.1 ± 1.6	24.4 ± 2.3^a
RBF (mL/min)	197 ± 19	163 ± 15^a	187 ± 20	239 ± 18^{a,b}
RVR (mm Hg·mL^{-1}·min^{-1})	0.48 ± 0.06	0.39 ± 0.12	0.46 ± 0.08	0.24 ± 0.07^{a,b}
E_{es} (mm Hg/mm)	13.8 ± 3.3	15.6 ± 4.4	14.8 ± 2.6	18.4 ± 4.9
VS (D) (mm/s)	−28.8 ± 6.6	−26.4 ± 3.3	−28.3 ± 5.2	−26.0 ± 4.0
% WT	14.9 ± 2.3	14.7 ± 2.6	15.0 ± 2.6	14.4 ± 2.1
WS (g/cm^2)	39.0 ± 5.0	17.8 ± 2.1^a	40.6 ± 5.3	33.0 ± 4.3^b
PRA (ng·mL^{-1}·h^{-1})	4.7 ± 1.0	11.9 ± 1.0^a	4.2 ± 1.5	20.4 ± 3.6^{a,b}
pH	7.37 ± 0.01	7.33 ± 0.01	7.38 ± 0.02	7.34 ± 0.03
Pco_2 (mm Hg)	40.0 ± 2.5	42.4 ± 1.7	39.6 ± 2.9	42 ± 2.8
Po_2 (mm Hg)	264 ± 35	137 ± 24^a	256 ± 29	262 ± 26^b

Values represent the mean ± SEM of eight dogs.

HR, heart rate; LVP, left ventricular pressure; MAP, mean arterial blood pressure; LVEDP, left ventricular end-diastolic pressure; CO, cardiac output; SV, stroke volume; SVR, systemic vascular resistance; RBF, renal blood flow measured by a calibrated flow probe; RVR, renal vascular resistance; E_{es}, slope of the left ventricular pressure-diameter relation; VS (D), velocity of shortening of LV diameter; % WT, percent of wall thickening; WS, left ventricular end-systolic meridional wall stress; PRA, plasma renin activity.

[a] $P < 0.05$ compared with baseline.

[b] $P < 0.05$ compared with nitroprusside.

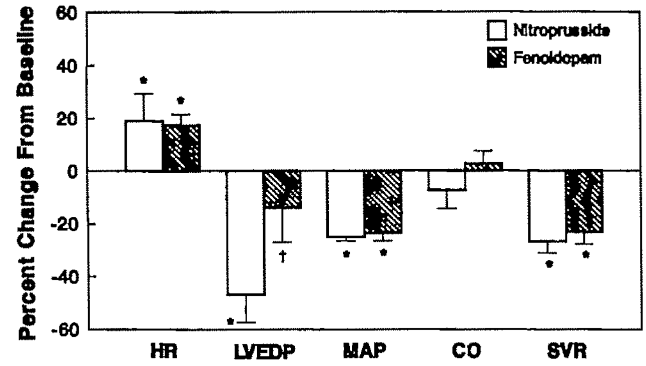


Figure 1. Hemodynamic changes from baseline in response to infusion of either fenoldopam or nitroprusside are compared. Except for a greater reduction in left ventricular end-diastolic pressure (LVEDP) with nitroprusside, changes in heart rate (HR), mean arterial blood pressure (MAP), cardiac output (CO), and systemic vascular resistance (SVR) are similar between agents. *Bars* represent mean ± SEM of eight dogs. $*P < 0.05$ compared with baseline. $†P < 0.05$ compared with nitroprusside.

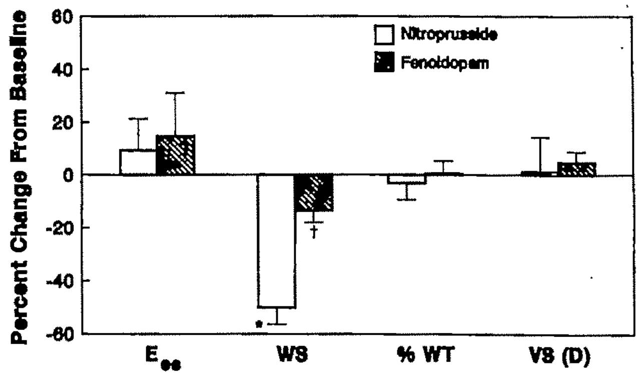


Figure 2. Comparison of myocardial performance during induced hypotension by either fenoldopam or nitroprusside. Changes are in percent from baseline. Myocardial performance assessed by the slope E_{es} of the left ventricular end-systolic pressure-diameter relationship, percent of wall thickening (%WT), and velocity of shortening of left ventricular diameter [VS(D)] does not change significantly with either drug. Left ventricular end-systolic wall stress (WS) decreases significantly more with nitroprusside than with fenoldopam. Bars represent mean ± SEM of eight dogs. $*P < 0.05$ compared with baseline. $†P < 0.05$ compared with nitroprusside.

myocardial oxygen supply to demand expressed by endocardial blood flow over wall stress increased significantly with both fenoldopam and nitroprusside, and a greater ($P < 0.05$) increase was observed with nitroprusside than fenoldopam. Regional blood flow distribution, expressed as percent change from baseline, showed similar decreases in blood flow to the spleen, whereas blood flow to the brain, small intestine, and skin did not change significantly with either drug. A twofold increase in hepatic arterial blood flow was observed with nitroprusside. In contrast, there were significant decreases in blood flow to the hepatic artery and muscle beds with fenoldopam (Figure 3).

Figure 4 shows regional distribution of blood flow to the renal bed as percent change from baseline. Renal perfusion decreased significantly with nitroprusside, whereas it increased with fenoldopam. Blood flow to the medulla, compared to the cortex,

Table 2. Effects of Nitroprusside and Fenoldopam on Blood Flow Distribution

	Baseline	Nitroprusside	Baseline	Fenoldopam
Skin	2.8 ± 0.4	2.0 ± 0.4	2.9 ± 0.6	2.6 ± 0.5
Muscle	4.7 ± 0.3	5.4 ± 0.5	4.5 ± 0.6	3.1 ± 0.4[b]
Liver (arterial flow)	14.7 ± 3.8	24.6 ± 4.8[a]	13.8 ± 4.5	6.4 ± 1.9[a,b]
Spleen	198 ± 34	124 ± 11[a]	226 ± 20	128 ± 9[a]
Right atrium	78 ± 13	74 ± 17	81 ± 11	77 ± 8
LV endocardium	88 ± 11	92 ± 10	95 ± 10	85 ± 5
LV epicardium	78 ± 8	83 ± 9	85 ± 7	78 ± 5
LV septum	73 ± 7	71 ± 7	79 ± 7	70 ± 5
Right ventricle	59 ± 4	60 ± 5	65 ± 5	61 ± 4
Small intestine	60 ± 7	63 ± 10	66 ± 10	76 ± 10
Kidney cortex	673 ± 39	558 ± 32[a]	649 ± 44	804 ± 42[a,b]
Kidney medulla	74 ± 13	63 ± 10	71 ± 10	92 ± 9[a,b]
Brain	57 ± 5	57 ± 3	55 ± 5	50 ± 5
Endo/Epi	1.09 ± 0.05	1.19 ± 0.05	1.12 ± 0.06	1.15 ± 0.07
Endo/WS	2.91 ± 0.53	6.40 ± 1.54[a]	2.90 ± 0.62	3.40 ± 0.69[b]

Values represent the mean ± SEM in $mL \cdot min^{-1} \cdot 100\ g^{-1}$ of eight dogs.

LV, left ventricular; Endo/Epi, endocardium/epicardium blood flow ratio; Endo/WS, endocardial blood flow/left ventricular end-systolic meridional wall stress ratio.

[a] $P < 0.05$ compared with baseline.

[b] $P < 0.05$ compared with nitroprusside.

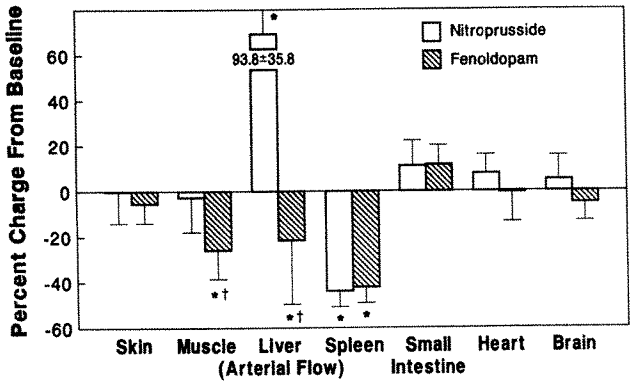
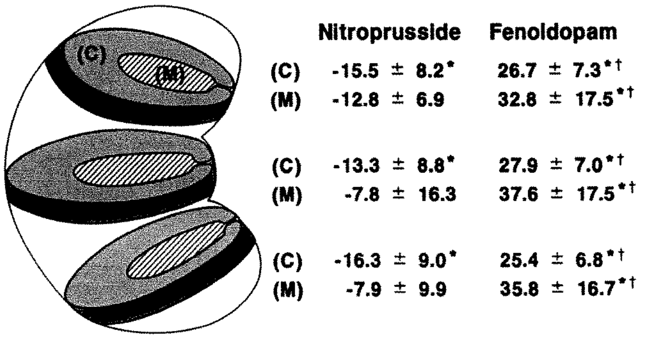


Figure 3. Changes in regional blood flow distribution in response to fenoldopam and nitroprusside are compared. Note similar reductions in splenic blood flow between the two drugs and significant decreases in blood flow to the muscle and liver (arterial flow) during fenoldopam infusion as compared with nitroprusside. Bars present mean ± SEM of eight dogs. *$P < 0.05$ compared with baseline. †$P < 0.05$ compared with nitroprusside.



	Nitroprusside	Fenoldopam
(C)	-15.5 ± 8.2*	26.7 ± 7.3*†
(M)	-12.8 ± 6.9	32.8 ± 17.5*†
(C)	-13.3 ± 8.8*	27.9 ± 7.0*†
(M)	-7.8 ± 16.3	37.6 ± 17.5*†
(C)	-16.3 ± 9.0*	25.4 ± 6.8*†
(M)	-7.9 ± 9.9	35.8 ± 16.7*†

Figure 4. Comparison of renal blood flow distribution during hypotension induced by either fenoldopam or nitroprusside. Changes are in percent from baseline with negative signs representing decreases. Cross sections of different regions of the right kidney are divided into cortex (C) and medulla (M). Renal perfusion decreases with nitroprusside, whereas it increases with fenoldopam. Values are mean ± SEM. *$P < 0.05$ compared with nitroprusside. †$P < 0.05$ compared with fenoldopam.

demonstrated a trend toward higher increases with fenoldopam and smaller decreases with nitroprusside. The changes in renal perfusion induced by either fenoldopam or nitroprusside did not vary when measured from the upper, middle, or lower regions of the kidney.

Discussion

Data from this study in dogs demonstrate that fenoldopam is as effective as nitroprusside in lowering arterial blood pressure to 60 mm Hg. Fenoldopam-induced hypotension was rapid in onset and abated quickly upon termination of infusion. Despite similar levels of hypotension, different regional blood flow distributions were demonstrated between the two agents. In particular, hypotension induced by fenoldopam was characterized by a selective 28% *increase* in renal perfusion without significant changes in coronary and cerebral blood flow or cardiac performance.

The reduction in arterial blood pressure with either drug was attributed to a decrease in vascular resistance owing to a direct peripheral vasodilation (7). Because fenoldopam does not cross the blood-brain barrier (12,13), the hypotensive effect of fenoldopam is restricted to peripheral activity. Unlike nitroprusside, which acts as a nonspecific direct dilator on arterial resistance vessels (14), fenoldopam induces relaxation of vascular smooth muscle by activation of postsynaptic DA_1 receptors. This vasodilator effect of fenoldopam is reported to be independent of α-adrenergic, β-adrenergic, cholinergic, or histaminergic receptors, or of catecholamine release (2,13). The venodilator effect of fenoldopam appears to be less intense than that of nitroprusside. At equal hypotensive level, a significantly lower LV end-diastolic pressure was observed with nitroprusside than fenoldopam, indicating a greater venodilation and reduced venous return with nitroprusside (15). Fenoldopam-induced hypotension was not accompanied by increased pulmonary shunting. Arterial oxygen tension remained constant during systemic hypotension with fenoldopam, in contrast to the nearly 50% decrease seen with nitroprusside.

Recently, assessment of cardiac contractility has included analysis of the LV end-systolic pressure-diameter relationship. This analysis provides an index of contractility that is highly sensitive to inotropic changes (9–11). Whether this index remains reliable in extreme loading conditions is subject to controversy (16,17). In the present study, other indices of contractility including percent of systolic shortening and velocity of shortening were also used to support the analysis. The results show that cardiac contractility was not significantly altered during 40 min of stable hypotension with either agent. In contrast, Ventura et al. (3) reported increases in LV ejection rate and velocity of circumferential fiber shortening in hypertensive patients treated with fenoldopam. However, these changes were not attributed to a direct positive inotropic effect of the drug. Instead, afterload reduction and activation of baroreceptors were thought to be responsible for reflex stimulation of the heart. This explanation agrees with an earlier report demonstrating an absence of inotropic effect of fenoldopam on isolated papillary muscle (13).

In the present study, hypotension induced by both drugs was accompanied by a gradual increase in heart rate. Nitroprusside maintains normal heart rate at moderate levels of hypotension (7,18). However, when the cumulative dose of nitroprusside increased, heart rate increased through enhanced sympathetic activity (19,20). Similarly, tachycardia associated with fenoldopam may be due to baroreceptor activation in response to hypotension. Interestingly, increases in heart rate were not observed when fenoldopam was infused in dogs anesthetized with pentobarbital (13) or was infused over a shorter duration (21).

Cerebral and coronary blood flows did not change during infusion of either fenoldopam or nitroprusside, suggesting that autoregulatory mechanism in these organs remained intact at this level of hypotension. On the other hand, RBF decreased after 40 min of nitroprusside infusion. The decrease in renal perfusion was similar to those previously reported at equal or lower levels of hypotension (18,21–23). With less severe hypotension and a shorter duration of nitroprusside infusion, there was a trend toward an increase in RBF (7,24). These findings support the theory that despite the dependence of RBF on perfusion pressure, blood flow to the renal bed may be related to level of hydration and reflex stimulation of sympathetic vasoconstrictor nerves (18,22). In contrast, fenoldopam significantly increased RBF by decreasing renal vascular resistance. Our results show a trend favoring a larger increase in medullary over cortical blood flows. This trend, although not reaching statistical significance, could be related to the regulation of medullary tonicity for the maintenance of Na^+ balance in the kidney. Nevertheless, the marked increases in RBF explain the increases in urine and Na^+ excretions reported in normal or hypertensive patients treated with fenoldopam (4,25). Fenoldopam is known to act specifically on DA_1 receptors. These receptors are located in abundance in the renal bed and to a lesser extent in the splanchnic bed, and their activation leads to a marked reduction in vascular smooth muscle tone (2,6,13). Although the renal vasodilation caused by fenoldopam is mainly mediated by the postsynaptic DA_1 receptors, whether presynaptic DA_1 receptors are also involved in the vascular activity of this drug remains controversial (13,26).

Fenoldopam infusion was accompanied by increased PRA that was significantly greater than that observed with nitroprusside. This increased PRA may account for increases of fenoldopam doses in two dogs to counteract vasoconstrictor effects caused by activation of the renin-angiotensin system. Whereas the increase in PRA may often be viewed as a compensatory response to systemic hypotension (27), fenoldopam-induced increases in PRA have been reported in the absence of blood pressure changes. Moreover, enhanced PRA persisted when fenoldopam was infused into the renal artery of ganglionic-blocked dogs or dogs in which the renal vasculature was maximally dilated (28). These findings strongly support the postulate that fenoldopam increases PRA by stimulating specific DA_1 receptors located at the juxtaglomerular cells (29,30). Nevertheless, despite elevated PRA, increments of RBF were probably mediated through dilation of renal vasculature secondary to activation of postsynaptic DA_1 receptors as well as through inhibition of vasoconstriction via presynaptic mechanisms. Absence of rebound hypertension after fenoldopam suggests that the increase in PRA rapidly abates after termination of infusion.

In summary, the results of this study show similar effectiveness in induction of hypotension by either fenoldopam or nitroprusside. These hypotensive drugs decreased arterial blood pressure by decreasing vascular resistance, but differences emerged when examining effects on regional blood flow. Importantly, RBF increased significantly with fenoldopam, whereas blood flow to other vital organs was well maintained. This renal vasodilator property may be particularly useful when renal perfusion should be protected during induced hypotension. However, owing to the increase in PRA associated with fenoldopam, angiotensin-converting enzyme inhibitors may be needed with fenoldopam for maintaining stable hypotension when longer infusion periods are necessary. Further study seems warranted for the evaluation of the combination of an angiotensin-converting enzyme inhibitor and fenoldopam, as fenoldopam, because of its selective (especially renal) effects, holds promise for clinical use as a hypotensive agent.

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References

1. Adams AP. Techniques of vascular control for deliberate hypotension during anaesthesia. Br J Anaesth 1971;47:777–92.
2. Goldberg LI. Dopamine and new dopamine analogs: receptors and clinical applications. J Clin Anaesth 1988;1:66–74.
3. Ventura HO, Messerli FH, Frohlich ED, et al. Immediate hemodynamic effects of a dopamine-receptor agonist (fenoldopam) in patients with essential hypertension. Circulation 1984;69:1142–5.
4. Murphy MH, McCoy CE, Weber RR, Frederickson ED, Douglas FL, Goldberg LI. Augmentation of renal blood flow and sodium excretion in hypertensive patients during blood pressure reduction by intravenous administration of the dopamine 1 agonist fenoldopam. Hypertension 1987;76:1312–8.
5. Elliott WJ, Weber RR, Nelson KS, et al. Renal and hemodynamic effects of intravenous fenoldopam versus nitroprusside in severe hypertension. Circulation 1990;81:970–7.
6. Goldberg LI, Rajfer SI. Dopamine receptors: applications in clinical cardiology. Circulation 1985;72:245–8.
7. Kien ND, White DA, Reitan JA, Eisele JH Jr. Cardiovascular function during controlled hypotension induced by adenosine triphosphate or sodium nitroprusside in the anesthetized dog. Anesth Analg 1987;66:103–10.
8. Colan SD, Borow KM, Neumann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load-independent index of myocardial contractility. J Am Coll Cardiol 1984;4:715–24.
9. Mahler F, Covell JW, Ross J Jr. Systolic pressure-diameter relations in the normal conscious dog. Cardiovasc Res 1975;9:447–55.
10. Sagawa K. The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use. Circulation 1981;63:1223–7.
11. Little WC, Freeman GL, O'Rourke RA. Simultaneous determination of left ventricular end-systolic pressure-volume and pressure-dimension relationships in closed-chest dogs. Circulation 1985;71:1301–8.
12. Goldberg LI. Dopamine receptors and hypertension. Physiologic and pharmacologic implications. Am J Med 1984;77:37–44.
13. Hahn RA, Wardell JR, Sarau HM, Ridley PT. Characterization of the peripheral and central effects of SK&F 82526, a novel dopamine receptor agonist. J Pharmacol Exp Ther 1982;223:305–13.
14. Miller RR, Fennell WH, Young JB, Palomo AR, Quinoner MA. Differential systemic arterial and venous actions and consequent cardiac effects of vasodilator drugs. Prog Cardiovasc Dis 1982;24:353–9.
15. Pouleur H, Covell JW, Ross J Jr. Effects of nitroprusside on venous return and central blood volume in the absence and presence of heart failure. Circulation 1980;61:328–37.
16. Little WC, Cheng C-P, Peterson T, Vinten-Johansen J. Response of the left ventricular end-systolic pressure-volume relation in conscious dogs to a wide range of contractile states. Circulation 1988;78:736–45.
17. Su JB, Crozatier B. Preload-induced curvilinearity of left ventricular end-systolic pressure-volume relations. Effects on derived indexes in closed-chest dogs. Circulation 1989;79:431–40.
18. Colley PS, Sivarajan M. Regional blood flow in dogs during halothane anesthesia and controlled hypotension produced by nitroprusside or nitroglycerin. Anesth Analg 1984;63:503–10.
19. Bloor BC, Fukunaga AF, Ma C, et al. Myocardial hemodynamics during induced hypotension: a comparison between sodium nitroprusside and adenosine triphosphate. Anesthesiology 1985;63:517–25.
20. Sivarajan M, Amory DW, McKenzie SM. Regional blood flows during induced hypotension by nitroprusside or trimethaphan in rhesus monkey. Anesth Analg 1985;64:759–66.
21. Aronson S, Goldberg LI, Roth S, Glock D, Moss J, Roizen MF. Preservation of renal blood flow during hypotension induced with fenoldopam in dogs. Can J Anaesth 1990;37:380–4.
22. Crystal GJ, Salem MR. Myocardial and systemic hemodynamics during isovolemic hemodilution alone and combined with nitroprusside-induced controlled hypotension. Anesth Analg 1991;72:227–37.
23. Zäll S, Edén E, Winsö I, Volkmann R, Sollevi A, Ricksten S-E. Controlled hypotension with adenosine or sodium nitroprusside during cerebral aneurysm surgery: effects on renal hemodynamics, excretory function, and renin release. Anesth Analg 1990;71:631–6.
24. Finegan BA, Chen H-J, Singh YN, Clanachan AS. Comparison of hemodynamic changes induced by adenosine monophosphate and sodium nitroprusside alone and during dopamine infusion in the anesthetized dog. Anesth Analg 1990;70:44–52.
25. Hughes JM, Beck TR, Rose CE, Carey RM. The effects of selective dopamine 1 receptor stimulation on renal and adrenal function in man. J Clin Endocrinol Metab 1988;66:518–25.
26. Lokhandwala MF, Jandhyala BS. The role of sympathetic nervous system in the vascular actions of dopamine. J Pharmacol Exp Ther 1979;210:120–6.
27. Mirenda JV, Grissom TE. Anesthetic implications of the renin-angiotensin system and angiotensin-converting enzyme inhibitors. Anesth Analg 1991;72:667–83.
28. Montier F, Katchadourian P, Pratz J, Cavero I. Increase in plasma renin activity evoked by fenoldopam in dogs is directly mediated by dopamine$_1$ receptor stimulation. Cardiovasc Pharmacol 1989;13:739–47.
29. Kurtz A, Della Bruna R, Pratz J, Cavero I. Rat juxtaglomerular cells are endowed with DA-1 dopamine receptor mediating renin release. Cardiovasc Pharmacol 1988;12:658–63.
30. Antonipillai I, Broers MI, Lang D. Evidence that specific dopamine-1 receptor activation is involved in dopamine-induced renin release. Hypertension 1989;13:463–8.

Systemic and Regional Hemodynamics of Isoflurane and Sevoflurane in Rats

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The authors studied the effects of sevoflurane and isoflurane on systemic hemodynamics and regional blood flow distribution (microsphere technique) in 15 rats during general anesthesia with intravenous chloralose and controlled ventilation. Inhaled anesthetics were applied to reduce mean arterial blood pressure (MAP) to 70 mm Hg (1.66 vol% sevoflurane and 0.96 vol% isoflurane) and 50 mm Hg (MAP 50; 3.95 vol% sevoflurane and 2.43 vol% isoflurane). Control recordings were obtained with intravenous chloralose only. At a MAP of 70 mm Hg, both anesthetics reduced heart rate, cardiac output, and systemic vascular resistance to a similar degree. Isoflurane decreased systemic vascular resistance markedly at a MAP of 50 mm Hg and thereby maintained cardiac output at higher levels than sevoflurane. The left ventricular rate-pressure product decreased comparably with both anesthetics. Cerebral blood flow increased dose-dependently with both inhaled anesthetics but to a greater degree with isoflurane. Total hepatic blood flow remained unchanged from control at a MAP of 70 mm Hg but decreased at a MAP of 50 mm Hg. This was due to reductions of hepatic arterial and portal venous tributaries. Renal blood flow was reduced with only the high concentrations of the anesthetics. Myocardial blood flow was reduced at all concentrations of volatile anesthetic; however, the decrease was less with isoflurane. This would indicate a more pronounced coronary vasodilation by isoflurane as the rate-pressure product, as a measure of the actual left ventricular oxygen demand, decreased by comparable degrees with both anesthetics. Our results indicate that sevoflurane and isoflurane (each approximately 0.7 MAC) have no dissimilar systemic and regional hemodynamic effects at a MAP of 70 mm Hg in this animal model. At higher concentrations (approximately 1.7 MAC), cerebral blood flow was more with isoflurane than with sevoflurane and was associated with a more pronounced vasodilation in the myocardium.

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In common with the other halogenated volatile anesthetics, sevoflurane causes dose-related cardiovascular depression (1–4) and thereby affects blood flow to various organs and tissues. Manohar and Parks (1) have investigated regional blood flow distribution during sevoflurane administration in chronically instrumented pigs. However, their use of sevoflurane as a single anesthetic is not routine in clinical practice. Rather, combinations of different anesthetics are used in patients to diminish the undesired side effects of each substance. Furthermore, detailed comparisons of regional blood flow during the administration of sevoflurane versus other presently used anesthetics are not available.

The cardiovascular effects of sevoflurane have recently been compared with those of isoflurane in chronically instrumented dogs (3). It was found that the effects of both agents on cardiac function and circulation were almost identical. This would render isoflurane the appropriate reference against which to compare sevoflurane. Hence, our study was designed to assess the effects of sevoflurane and isoflurane on systemic hemodynamics and regional organ blood flow. Investigations were performed in rats during basal anesthesia and the volatile anesthetics were used to deepen anesthesia and to control systemic hemodynamics. Comparisons were made at identical levels of mean arterial blood pressure (MAP).

Methods

Animals and Experimental Preparation

After approval had been obtained from the local animal care committee, 15 male Sprague-Dawley rats

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(aged 2–3 wk, mean body weight 299 ± 8 g; Savo, Kisslegg, Germany) were used to determine the influence of sevoflurane and isoflurane on systemic and regional hemodynamics. The animals were anesthetized with chloral hydrate administered intraperitoneally, after which a tracheotomy was performed. Controlled ventilation with oxygen in room air was provided by a small animal ventilator (Harvard 683, Harvard Apparatus, South Natick, Mass.) inserted through the tracheal tube. The inspiratory oxygen fraction was adjusted to maintain Pa_{O_2} between 110 and 120 mm Hg. At a rate of 50–55 breaths/min, tidal volume was set to keep Pa_{CO_2} at 35 mm Hg. Adequate anesthesia was maintained throughout the experiments by intravenous infusion of α-chloralose (stock solution: 20 mg borax and 20 mg chloralose dissolved in 1 mL saline; 2 $mg \cdot 100\ g^{-1} \cdot h^{-1}$). The volatile anesthetics were administered by means of previously calibrated standard vaporizers (Dräger, Lübeck, Germany).

The animals were placed on a heating pad to maintain rectal temperature at 37°C. The right femoral artery was exposed through a cutdown, and a polyethylene tubing was inserted for determination of arterial blood pressure and for withdrawal of blood samples for blood gas analyses. Another catheter inserted into the vena cava superior through the right jugular vein was used for determination of the central venous pressure and for intravenous infusion of saline solution and of drugs. Saline solution was infused throughout the experiment at a rate of 2.5 $mL \cdot kg^{-1} \cdot h^{-1}$. A highly flexible polyethylene catheter was inserted into the left ventricle through the right carotid artery. Correct position of this catheter was verified continuously by pressure monitoring. Finally, a catheter was inserted into the tail artery for withdrawal of reference samples during microsphere injections. The femoral arterial, left ventricular, and central venous pressure cannulas were connected to standard small-animal pressure transducers, and all signals were recorded continuously. Heart rate was obtained from the electrocardiogram. The left ventricular rate-pressure product as a measure of left ventricular oxygen demand was obtained by multiplying heart rate and mean arterial blood pressure.

The reference withdrawal method was applied to measure organ blood flow and cardiac output with radioactive microspheres (5). We used standard carbonized microspheres with a mean diameter of 15 μm, labeled with ^{141}Ce, ^{51}Cr, ^{85}Sr, ^{95}Nb, and ^{46}Sc (3M Company, St. Paul, Minn.). The microspheres were suspended in hydroxy ethyl starch (mol wt 40,000) to retard sedimentation, with 0.01% polysorbate (Tween 80) added as a detergent to prevent aggregation. We used high molecular weight starch as a suspension medium to maintain a homogeneous solution of spheres before injection, because dextran used as suspension medium was shown to cause significant hypotension in Sprague-Dawley rats (6).

Approximately 100,000 microspheres suspended in a volume of 0.3 mL were injected into the left ventricle using a syringe for each blood flow determination. Injection was accomplished within 20 s, and the catheter was subsequently flushed with 0.4 mL of warmed saline solution. An arterial reference sample was withdrawn at a flow rate of 0.62 mL/min. Withdrawal was started 10 s before microsphere injection and continued for 40 s thereafter (7). The withdrawal of 0.6 mL of blood for the arterial reference sample is approximately equal to 5% of a rat's blood volume (8). In agreement with results from others, this mild hemorrhage was well tolerated (6). To further reduce the impact of repeated blood sampling, the sequence of experimental steps was strictly randomized. As variations in microsphere diameters would impose a systematic error on the results, the sequence of isotopes also was randomized. The rats were killed after the last microsphere injection by intravenous infusion of KCl, and the organs were removed, weighed, and placed in counting vials.

Radioactivity was determined in the heart, liver, pancreas, stomach, small and large intestine, spleen, and lungs. These organs were weighed and counted in toto. To verify accurate microsphere distribution, right and left kidneys and skeletal muscle samples were processed separately. As a routine in this laboratory, animals with a nonuniform distribution of microspheres manifested by differences between left and right kidney blood flows of greater than 10% are excluded from study. No animal of this series had to be eliminated for this reason. Because the catheter in the right carotid artery might interfere with microsphere distribution in the brain, cerebral blood flow was determined separately in both hemispheres. The number of microspheres trapped and regional blood flow were determined in each tissue and reference sample.

Cardiac output was calculated as total injected activity times reference sample flow divided by reference sample activity. The total injected activity and the corresponding number of microspheres were determined by subtraction of the residual activity in the injection syringe from its initial value. Radioactivity measurements were performed in a 1024-channel, multiple region-of-interest gamma counter with a 3-in crystal (5650, Packard Instruments, Downers Grove, Ill). Raw data were analyzed using a special designed software program (9). All data were corrected for background and cross-over activity. The relatively high number of microspheres injected assured that all tissue samples and the arterial reference

Table 1. Systemic Hemodynamics, Arterial Blood Gases, and Hemoglobin Concentrations

	Control	Sevoflurane MAP 70	Sevoflurane MAP 50	Isoflurane MAP 70	Isoflurane MAP 50
Vol%	0	1.66 ± 0.19	3.95 ± 0.21	0.96 ± 0.09	2.43 ± 0.21
MAP (mm Hg)	91 ± 3	70 ± 0	50 ± 1	70 ± 0	50 ± 0
CO (mL/min	114.1 ± 7.9	94.7 ± 6.2[a]	80.0 ± 6.2[a]	95.0 ± 5.1[a]	92.8 ± 4.9[a,b]
HR (min^{-1})	429 ± 9	382 ± 7[a]	355 ± 8[a]	395 ± 8[a]	365 ± 5[a]
SVR ($dyne \cdot s \cdot cm^{-5}$)	65.1 ± 5.2	58.9 ± 3.6	51.4 ± 5.3[a]	58.3 ± 3.8	39.3 ± 2.7[a,b]
RPP (mm Hg/min $\times 10^3$)	38.9 ± 1.5	26.7 ± 0.5[a]	17.8 ± 0.4[a]	27.6 ± 0.6[a]	18.2 ± 0.3[a]
Pa_{O_2} (mm Hg)	116 ± 2	113 ± 3	118 ± 3	114 ± 3	117 ± 4
Pa_{CO_2} (mm Hg)	36 ± 2	34 ± 3	33 ± 3	35 ± 3	34 ± 2
Hb (g/100 mL)	13 ± 1	14 ± 1	14 ± 1	14 ± 1	13 ± 1

MAP, mean arterial blood pressure; CO, cardiac output; HR, heart rate; SVR, systemic vascular resistance; RPP, rate-pressure product; Pa_{O_2}, arterial oxygen tension; Pa_{CO_2}, arterial carbon dioxide tension; Hb, hemoglobin concentration; MAP 70, mean arterial blood pressure of 70 mm Hg; MAP 50, mean arterial blood pressure of 50 mm Hg.

Results are given as mean ± SEM; $n = 15$.

[a] $P < 0.05$ versus control.

[b] $P < 0.05$ versus second gas (sevoflurane/isoflurane MAP 70, sevoflurane/isoflurane MAP 50).

samples contained the required minimum of 400 spheres. This provided a good accuracy of blood flow determinations (10,11) and guaranteed that even the low flow values of organs such as skeletal muscle could be measured with sufficient precision.

Portal venous blood flow was estimated as the sum of flows through the stomach, pancreas, spleen, and small and large intestine (12). Preportal resistance was calculated as the quotient from the mean arterial to portal venous pressure difference and portal flow, assuming a portal venous pressure of 10 mm Hg (13). Systemic shunt of microspheres was obtained by the following formula: activity detected in the lungs ÷ total injected activity × 100.

Each protocol included a control period, where only the intravenous background anesthetic was infused, and four experimental steps with MAP lowered to 70 and 50 mm Hg by either isoflurane or sevoflurane. The control recording and hypotension by volatile anesthetics were randomized. When an experiment started with hypotension by a volatile anesthetic, MAP was adjusted to 70 or 50 mm Hg immediately after the surgical preparation period and measurements started after 30 min of stable hemodynamic conditions. Recordings of hemodynamics and blood gas parameters were obtained first, followed by injection of radioactive microspheres. The animals were allowed to recover without volatile anesthetic for at least 15 min. Mean arterial blood pressure was then lowered by the next agent or concentration. Control recordings were performed after no volatile anesthetic had been given for at least 30 min.

Results are expressed as mean ± SEM. Differences among experimental conditions were evaluated by the Friedman ranked analysis of variance. This was followed by Wilcoxon and Wilcox multiple comparisons to determine which experimental steps were significantly different from each other. A P value less than 0.05 was considered statistically significant.

Results

Results for systemic hemodynamics, arterial blood gases, and hemoglobin concentrations are summarized in Table 1. Those for organ blood flow and the distribution of cardiac output are given in Tables 2 and 3, respectively. Changes in selected organ blood flows and vascular resistances are illustrated in Figures 1–3.

During control, heart rate was 429 ± 9 beats/min and MAP was 91 ± 3 mm Hg. Mean arterial blood pressure was decreased to 70 and 50 mm Hg by 1.66 ± 0.19 and 3.95 ± 0.21 vol% sevoflurane and 0.96 ± 0.09 and 2.43 ± 0.21 vol% isoflurane, respectively. This led to significant decreases in heart rate with both anesthetics. Cardiac output at a MAP of 70 mm Hg was reduced by both anesthetics comparably. At a MAP of 50 mm Hg, cardiac output was significantly more during isoflurane than during sevoflurane administration. This was due to a significantly greater decrease of systemic vascular resistance with isoflurane. Because of comparable decreases in MAP and heart rate, the left ventricular rate-pressure product dropped almost identically with sevoflurane and isoflurane. Central venous pressure was 4–6 mm Hg throughout the study. Arterial blood gases and hemoglobin concentrations remained within the control range throughout the experiments (Table 1).

Myocardial blood flow decreased dose-dependently with sevoflurane and isoflurane, but to a greater degree with sevoflurane. Coronary vascular resistance at a MAP of 70 and 50 mm Hg decreased by 4% and 25% during sevoflurane and by 15% and 36%

Table 2. Regional Blood Flow During Sevoflurane and Isoflurane Administration

Blood flow ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	Control	Sevoflurane		Isoflurane	
		MAP 70	MAP 50	MAP 70	MAP 50
Heart	601 ± 62	498 ± 43[a]	443 ± 37[a]	542 ± 62	504 ± 85
Brain	108 ± 12	94 ± 8	106 ± 7	119 ± 9	132 ± 7[a,b]
Left hemisphere	106 ± 11	93 ± 8	110 ± 7	119 ± 9	142 ± 8[a,b]
Right hemisphere	109 ± 11	93 ± 7	102 ± 6	117 ± 8	121 ± 7[a,b]
Total liver	204 ± 16	190 ± 12	163 ± 10[a]	200 ± 14	173 ± 9[a]
Hepatic artery	37 ± 6	36 ± 5	26 ± 3	40 ± 5	25 ± 3
Portal vein	167 ± 12	154 ± 10	136 ± 8[a]	160 ± 10	146 ± 6[a]
Pancreas	105 ± 12	79 ± 7[a]	93 ± 10	82 ± 11[a]	139 ± 8[a,b]
Spleen	293 ± 44	259 ± 37	200 ± 25[a]	345 ± 40	120 ± 17[a,b]
Stomach	83 ± 6	75 ± 6	78 ± 7	78 ± 6	100 ± 7[b]
Small intestine	176 ± 14	174 ± 16	151 ± 10	182 ± 14	164 ± 14
Large intestine	138 ± 9	122 ± 5	112 ± 9	126 ± 8	131 ± 8
Kidneys	436 ± 24	432 ± 18	353 ± 23[a]	453 ± 22	362 ± 37[a]
Left kidney	429 ± 24	421 ± 18	353 ± 20[a]	444 ± 22	358 ± 48[a]
Right kidney	442 ± 24	443 ± 18	352 ± 26[a]	460 ± 22	365 ± 31[a]
Psoas muscle	10 ± 1	11 ± 4	9 ± 1	8 ± 1	14 ± 3[b]
Femoral muscle	12.2 ± 1.1	8.7 ± 0.5	11.1 ± 1.4	8.9 ± 0.6	18.1 ± 3.9[b]

MAP 70, mean arterial blood pressure of 70 mm Hg; MAP 50, mean arterial blood pressure of 50 mm Hg.
Results are given as mean ± SEM; $n = 15$.

[a] $P < 0.05$ versus control.

[b] $P < 0.05$ versus second gas (sevoflurane/isoflurane MAP 70, sevoflurane/isoflurane MAP 50).

Table 3. Regional Blood Flow (% of cardiac outflow) During Sevoflurane and Isoflurane Administration

Blood flow (% of cardiac output)	Control	Sevoflurane		Isoflurane	
		MAP 70	MAP 50	MAP 70	MAP 50
Heart	5.2 ± 0.4	4.9 ± 0.3	5.4 ± 0.5	5.8 ± 0.6	5.6 ± 0.8
Brain	1.8 ± 0.1	1.9 ± 0.1	2.3 ± 0.2[a]	2.4 ± 0.2[a]	2.7 ± 0.2[a,b]
Total liver	23.8 ± 0.9	26.7 ± 0.8[a]	28.5 ± 2.3[a]	28.6 ± 2.0[a]	24.2 ± 1.2
Hepatic artery	4.2 ± 0.7	4.9 ± 0.6	4.5 ± 0.4	5.7 ± 0.7	3.3 ± 0.3[b]
Portal vein	19.6 ± 0.9	21.8 ± 1.1	23.9 ± 1.9[a]	22.9 ± 1.5[a]	20.9 ± 1.1
Pancreas	1.2 ± 0.1	1.1 ± 0.1	1.6 ± 0.2[a]	1.1 ± 0.1	1.9 ± 0.2[a,b]
Spleen	2.2 ± 0.5	2.1 ± 0.4	2.1 ± 0.4	2.5 ± 0.4	1.0 ± 0.2[a,b]
Stomach	1.1 ± 0.1	1.1 ± 0.1	1.4 ± 0.2[a]	1.1 ± 0.1	1.6 ± 0.1[a]
Small intestine	11.1 ± 0.8	13.0 ± 0.9	14.3 ± 1.5	13.9 ± 1.0	11.8 ± 0.7
Large intestine	4.0 ± 0.3	4.4 ± 0.4	4.6 ± 0.3	4.4 ± 0.3	4.6 ± 0.3
Kidneys	11.9 ± 0.6	14.2 ± 0.7[a]	14.4 ± 1.4[a]	14.8 ± 0.9[a]	11.1 ± 0.7[b]
Psoas muscle	0.7 ± 0.1	0.9 ± 0.4	0.9 ± 0.1	0.6 ± 0.1	0.9 ± 0.1
Femoral muscle	1.3 ± 0.1	1.1 ± 0.1	1.6 ± 0.2[a]	1.1 ± 0.1	1.8 ± 0.2[a]
Lungs	4.6 ± 0.9	4.4 ± 0.5	4.2 ± 0.5	3.8 ± 0.4	3.3 ± 0.3[b]

MAP 70, mean arterial blood pressure of 70 mm Hg; MAP 50, mean arterial blood pressure of 50 mm Hg.
Results are given as mean ± SEM; $n = 15$.

[a] $P < 0.05$ versus control.

[b] $P < 0.05$ versus second gas (sevoflurane/isoflurane MAP 70, sevoflurane/isoflurane MAP 50).

during isoflurane, respectively. Both values were significantly different from control at a MAP of 50 mm Hg (Figure 1). Also at that point, the fractions of cardiac output to the heart showed a tendency to increase.

Blood flow values to both cerebral hemispheres had been calculated separately. Flow varied randomly by approximately 5% between the hemispheres, but the right hemisphere (common carotid artery occluded) was not statistically different from the left hemisphere. The blood flow values were therefore matched to give the result for the whole brain. Total brain blood flow was 1.08 ± 0.12 $mL \cdot min^{-1} \cdot g^{-1}$ at control. Blood flow decreased slightly with sevoflurane, but increased with isoflurane. The increase by 22% with isoflurane was statistically significant at a MAP of 50 mm Hg, as were the reduction of cerebral vascular resistance (Figure 2)

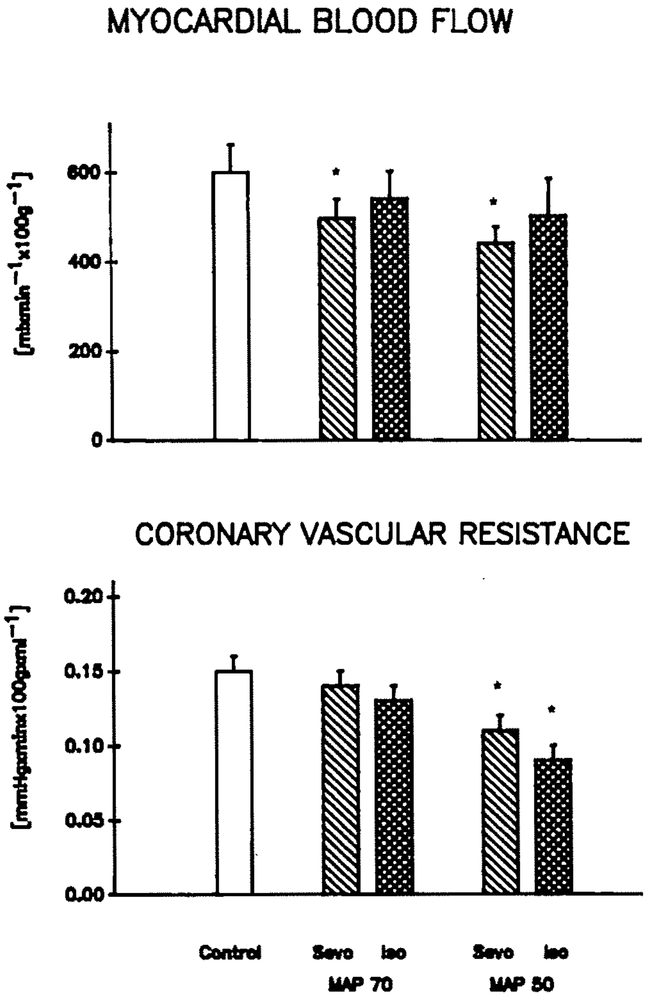

Figure 1. Myocardial blood flow and coronary vascular resistance during hypotension induced by sevoflurane and isoflurane (mean arterial blood pressure 70 and 50 mm Hg). All values are given as mean ± SEM; $n = 15$. *, $P < 0.05$ vs control.

and the increase of the fraction of cardiac output to the brain with both anesthetics.

Total flow to the liver was essentially unchanged from control at a MAP of 70 mm Hg with both anesthetics, but significantly decreased at a MAP of 50 mm Hg (−20% with sevoflurane; −15% with isoflurane). This decrease was due to a reduction of both the hepatic arterial inflow (−30% sevoflurane; −32% isoflurane and the portal venous flow (−19% sevoflurane; −13% isoflurane). Hepatic arterial flow varied considerably in the experiments, and hence changes did not reach the level of statistical significance. Within the preportal bed, most organs followed the behavior of portal flow: blood flow decreased slightly, whereas the fractions of cardiac output to these organs showed a tendency to increase. An exception was found in the pancreatic vascular bed where flow decreased at a MAP of 70 mm Hg with sevoflurane and isoflurane, but increased again at the higher anesthetic concentrations. During isoflurane administration at a MAP of 50 mm Hg, pancreatic perfusion significantly exceeded control values and the values at a MAP of 70 mm Hg. This was not due to major changes in only few animals, but rather to homogeneous responses of the pancreas, as evidenced from the narrow distribution of the data.

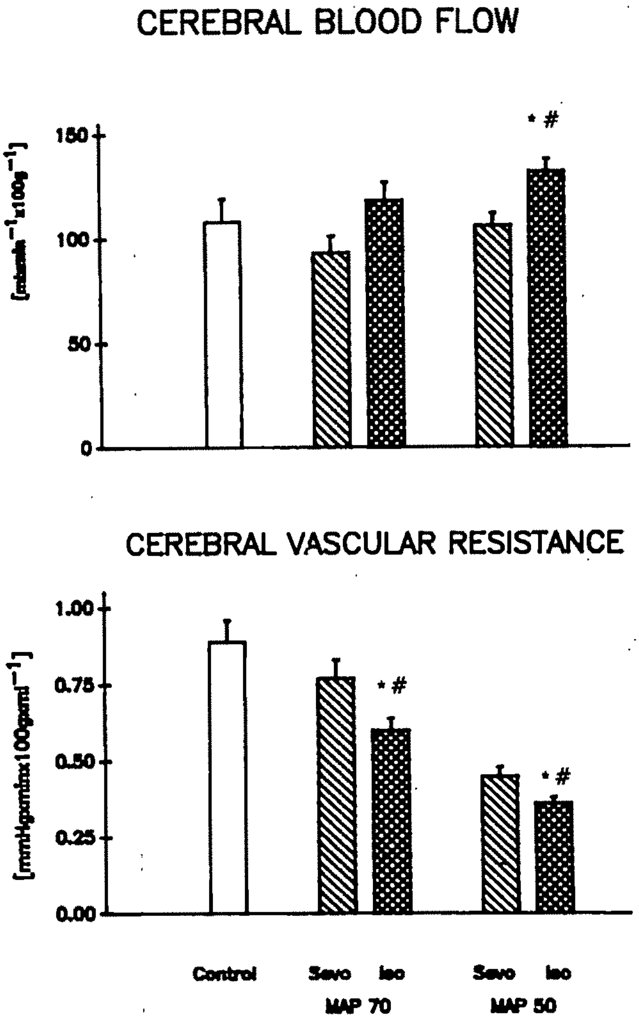

Figure 2. Cerebral blood flow and cerebral vascular resistance during hypotension induced by sevoflurane and isoflurane (mean arterial blood pressure 70 and 50 mm Hg). All values are given as mean ± SEM; $n = 15$. *, $P < 0.05$ vs control. #, $P < 0.05$ vs second gas.

In no experiment did left and right renal blood flow differ by more than 5%. Renal flow was well maintained at a MAP of 70 mm Hg, but perfusion decreased significantly at a MAP of 50 mm Hg with both anesthetics (−19% sevoflurane; −17% isoflurane). Renal vascular resistance was significantly lower than its control value at all steps involving volatile anesthetics (Figure 3).

The higher concentrations of both anesthetics ap-

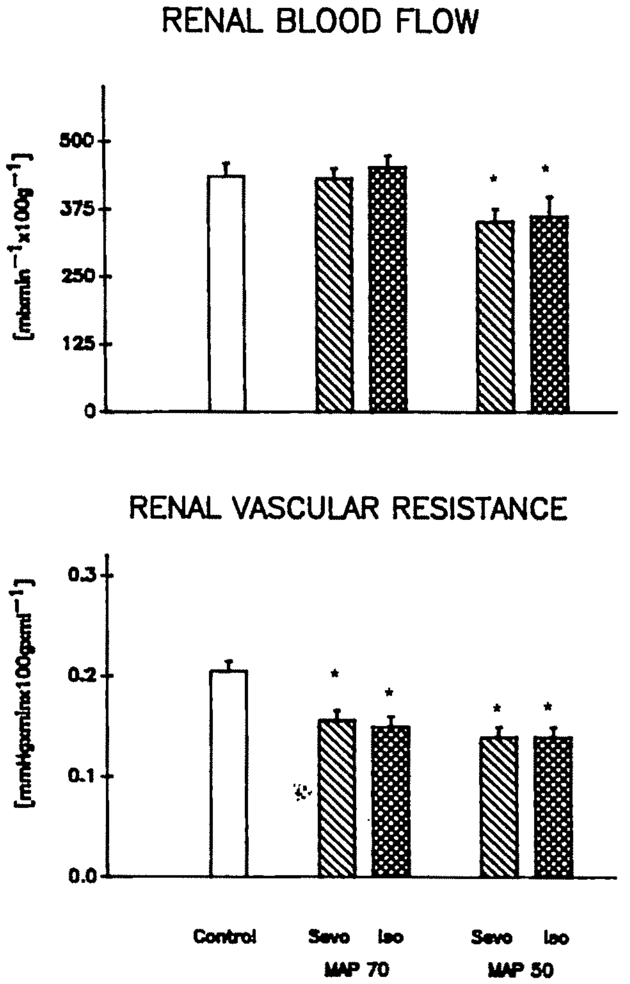

Figure 3. Renal blood flow and renal vascular resistance during hypotension induced by sevoflurane and isoflurane (mean arterial blood pressure 70 and 50 mm Hg). All values are given as mean ± SEM; $n = 15$. *, $P < 0.05$ vs control.

peared to dilate skeletal muscle resistance vessels (isoflurane more than sevoflurane). Radioactivity in the lungs was lower with volatile anesthetics as compared with control, indicating the absence of gross shunting of microspheres into the systemic circulation despite systemic vasodilation induced by these substances as indicated by the reduction of peripheral resistance.

Discussion

In this study, rats were given sevoflurane and isoflurane in the presence of a chloralose-based anesthetic. Using these anesthetics, MAP was reduced to 70 and 50 mm Hg. The results indicate that the inhaled anesthetics sevoflurane and isoflurane have very similar effects on systemic hemodynamic variables as well as on distribution of cardiac output. Assuming MAC values of 1.4 vol% for isoflurane (14) and 2.5 vol% for sevoflurane (15), we found virtually no difference between low doses of sevoflurane and isoflurane (0.7 MAC). However, at high concentrations of inhaled anesthetics (1.7 MAC), significant differences were observed. In comparison with sevoflurane, isoflurane increased cerebral, stomach, pancreas, and muscle blood flow, maintained cardiac output and myocardial perfusion, and decreased spleen blood flow.

For interpretation of the results, we adjusted the inspiratory concentrations of both anesthetics to achieve a preset hemodynamic response, namely MAPs of 70 and 50 mm Hg. We did this to mimic the clinical situation where volatile anesthetics are applied to control the patient's anesthetic depth together with arterial blood pressure rather than to obtain a defined cerebral gas tension (MAC multiple). However, with a MAC of 2.5% for sevoflurane and of 1.4 vol% for isoflurane, the concentrations of both anesthetics finally applied to the rats would indicate that in fact equipotent hemodynamic as well as cerebral concentrations had been applied (Table 1).

At control, the values for heart rate, MAP, and cardiac output were similar to those observed in conscious animals (13,16). Both anesthetics dose-dependently reduced MAP and cardiac output owing to the cardiodepressant properties inherent to all halogenated anesthetic vapors (17,18). The low concentrations of isoflurane and sevoflurane reduced cardiac output, heart rate, and systemic vascular resistance by similar extents, which would permit speculation that they depressed cardiac function by comparable degrees. At the high concentration, however, cardiac output was significantly greater with isoflurane. This difference was mainly caused by peripheral vasodilation and reduced left ventricular afterload, as systemic vascular resistance was considerably decreased by isoflurane. The left ventricular rate-pressure product as a measure of left ventricular oxygen demand decreased comparably with both anesthetics.

In addition to the negative inotropic effect as suggested by decreases in stroke volume in this study, reduction of cardiac output was also due to a dose-dependent decrease of heart rate with both anesthetics. This finding appears to be in conflict with previously published results, where unchanged (1,19) or even increased heart rate (3) has been reported with these anesthetics. Besides differences in the experimental protocols and the species, our experiments were performed during continuous infusion of an intravenous anesthetic, which might interfere with the carotid sinus baroreceptor reflex response to compensate for blood pressure reduction by an increase in heart rate (20,21). This carotid sinus depression, in combination with the known calcium-antagonistic effects of halogenated anesthetics in the sinus node, would explain the decreases in heart rate (22).

The effects of sevoflurane and isoflurane on coronary perfusion have recently been studied in dogs (3) and in pigs (1,23). In contrast to findings in pigs (1), Bernard and coworkers (3) reported considerable reduction of calculated coronary vascular resistance during the application of either of the anesthetics. However, regulation of perfusion in the normal myocardium is known to be dependent on oxygen demand. Therefore, documentation of a disparity between myocardial oxygen supply and demand by measurement of oxygen in coronary venous blood would be a more appropriate indicator of pharmacologically induced vasodilation. Whereas coronary vasodilation has been documented for isoflurane by oxygen measurement in coronary venous blood (24, 25), such data are not available for sevoflurane. In this study, both anesthetics dose-dependently decreased coronary flow. A difference was obtained for both anesthetics, inasmuch as isoflurane decreased absolute coronary vascular resistance more than sevoflurane. With regard to this finding, our data do not exclude vasodilation beyond the myocardial metabolic needs for sevoflurane, and they do not prove excess coronary dilation with isoflurane. However, with regard to the rate-pressure product as a measure of the actual left ventricular oxygen demand, which was reduced to a comparable degree by sevoflurane and isoflurane, the slightly more pronounced decrease of coronary vascular resistance would be indicative of a relative overperfusion of the myocardium during isoflurane. Hence, although excess coronary vasodilation by sevoflurane cannot be excluded by our data, it appears that in this respect sevoflurane is less active than isoflurane.

Volatile anesthetics administered in concentrations above 0.6 MAC during normocapnia produce increases in cerebral blood flow (26). This drug-induced increase in perfusion occurs despite concomitant reductions in cerebral metabolic requirements. Anesthetic requirements in our rats were slightly above 0.6 MAC at a MAP of 70 mm Hg and considerably higher at a MAP of 50 mm Hg. In accordance with previously published results, we observed a slight increase of cerebral blood flow with isoflurane at a MAP of 70 mm Hg, which was more pronounced at the higher concentration. Vasodilation was also evident from the fraction of cardiac output to the brain, which increased significantly, while cerebral vascular resistance decreased. In contrast, sevoflurane did not increase cerebral blood flow above its control value, although its high concentration yielded higher flow values and a considerably increased fraction of cardiac output as compared with its low concentration.

In awake individuals, cerebral blood flow varies with oxygen demand. This coupling of the cerebral metabolic rate with oxygen supply is not abolished during anesthesia, although halogenated volatile anesthetics certainly interfere with the metabolic regulation of perfusion (27,28). Hence, metabolic differences between sevoflurane and isoflurane might have contributed to the differing effects of these anesthetics on cerebral blood flow. We cannot exclude this possibility because cerebral oxygen uptake was not determined in these experiments. However, there is evidence that isoflurane in end-expired concentrations of 3% causes maximal depression of oxygen consumption (29). A higher cerebral metabolic rate, therefore, appears an unlikely explanation for the differing blood flow values.

There has been some work published that among the presently used volatile anesthetics halothane has the most pronounced and isoflurane has the least cerebral vessel dilating properties (30–32). These results have been challenged recently, mainly for methodologic reasons (27). It was beyond the scope of this study to reevaluate presumed differences among the established halogenated anesthetics. Nevertheless, our results clearly show by measurement of total brain blood flow that sevoflurane is less active than isoflurane in the cerebral vascular bed. This finding might be of importance in patients with an elevated intracranial pressure and a reduced intracranial compliance.

Total hepatic blood flow was unchanged from control with both anesthetics at a MAP of 70 mm Hg. This was due to increased fractions of cardiac output to both portal venous and hepatic arterial tributaries. Isoflurane maintained portal flow slightly better than sevoflurane at a MAP of 50 mm Hg. Findings of an increased hepatic arterial inflow with isoflurane (33,34) could not be confirmed in the present study, although the hepatic arterial fraction of cardiac output increased and hepatic arterial resistance decreased significantly. Decreased hepatic arterial blood flow with isoflurane has also been described by others (17,35). Hence, sevoflurane and isoflurane dilate hepatic arterial resistance vessels. The extent of dilation certainly depends on additional factors (e.g., control values and background anesthesia). Both anesthetics also reduced preportal vascular resistance comparably, and there were only minor differences in flow values to different preportal organs.

One unexpected finding of this investigation was that pancreatic perfusion was well maintained at a MAP of 50 mm Hg, exceeding flow values obtained at the lower anesthetic concentrations. The high concentration of isoflurane even increased pancreatic perfusion over its control value (Table 2). Such increased perfusion was found in all animals except for two, thereby excluding an artifact by outliers. Although the reason for this behavior of pancreatic flow is not clear at present, extraordinary pancreatic vasodilation at low arterial pressures agrees with earlier findings from this laboratory for enflurane (36). In that study in rats, in agreement with the present study, splanchnic blood flow decreased by a comparable degree during enflurane, whereas pancreatic perfusion was unchanged from control at a MAP of 50 mm Hg. We cannot decide whether the maintainance of blood flow results from anesthetic-induced vasodilation or reflects intrinsic regulatory phenomena of the pancreatic vascular bed, i.e., autoregulation. We are not aware of detailed studies of pancreatic blood flow regulation during different experimental conditions. Studies in rats by other investigators reported maximum pancreatic flow values of 3–4 mL·min^{-1}·g^{-1} with papaverin and hence a considerable potency for vasodilation (37), or increased pancreatic flow during yohimbine- or propanolol-induced hypotension (38). Certainly the choice of the animal species could contribute to this result as sevoflurane (1 MAC) and isoflurane (1 and 2 MAC) induced a decrease in pancreatic perfusion in pigs and dogs (1,34). Further studies of pancreatic flow during other inhaled anesthetics in rats do not seem to be available. The reason and significance of this unexpected finding therefore remains to be elucidated.

Renal perfusion was well maintained with both anesthetics at a MAP of 70 mm Hg. As a consequence, the fraction of cardiac output to the kidneys was increased, and renal vascular resistance was significantly decreased. Sevoflurane and isoflurane reduced renal perfusion at a MAP of 50 mm Hg comparably. Autoregulation in the arterial pressure range between 80 and 180 mm Hg has long been known for halothane and has recently been shown for enflurane (39). Although at a MAP of 50 mm Hg, MAP was considerably below the autoregulation limit of rat kidney (40), we cannot decide whether maintained perfusion with the lower anesthetic concentrations was due to autoregulation at the edge of the autoregulation curve, to specific drug effects, or to both.

The significance of the results critically depends on the validity of the rat model for studies of regional blood flow distribution. The insertion of the left ventricular catheter through the right carotid artery might be expected to alter blood flow to the brain. Seyde and Longnecker (13) reported reduced blood flow to the right hemisphere in the presence of a cannula in the right carotid artery. However, it was shown by others that unilateral carotid cannulation in the rat did not significantly affect cerebral blood flow, suggesting that adequate blood flow must exist through the patent carotid artery and the vertebral vessels (41). In agreement, comparison of perfusion of left and right cerebral hemispheres in our study did not yield statistically significant differences.

All experiments were performed during the administration of steady-state intravenous background anesthesia. This was done to reproduce more closely the clinical situation where volatile anesthetics are used as a tool to adjust anesthetic depth to changing intraoperative conditions during balanced anesthetic regimens. Furthermore, background anesthesia enabled controlled ventilation of the lungs not only during application of the volatile anesthetics but also during the period without these anesthetics (which we defined as control). Mechanical ventilation is essential during administration of volatile anesthetics to maintain normal arterial blood gases and to avoid interference of alveolar hypoventilation by the anesthetics, i.e., hypoxemia and hypercapnia. Also, continuous ventilation avoided the well-documented alterations by onset of intermittent positive pressure ventilation on the circulation, so that the addition of a volatile anesthetic remained the only difference in comparison with the control recording.

We do not assume that background anesthesia had a pronounced effect on the rat cardiovascular system. Results from systemic hemodynamic variables and regional blood flow are in good agreement with those obtained in awake rats (13). The intravenous anesthetic certainly decreased the MAC values of sevoflurane and isoflurane by an unknown extent. However, decreases of MAC requirements should be comparable for both anesthetics as chloralose was infused at an unchanged rate throughout the experiments, providing a constant depth of background anesthesia. Because of the small respiratory tidal volume, alveolar concentrations of the anesthetics could not be measured. It is probable that inspired and end-expiratory concentrations were close to unity during the measurement. This is inferred from our own studies in larger animals, where the technique of beginning an experimental step with a very high gas concentration that is reduced successively leads to equilibration of inspired and end-expired concentrations in a fairly short period.

Although it is obviously tenuous to transfer results from one species to another, it is appropriate to question whether the rat is a reasonable model to study hemodynamic influences of anesthetics in humans. The effects of isoflurane are well documented in humans, but the effects of sevoflurane are less clear. In humans, as in our rat model, isoflurane reduces MAP by its negative inotropic effects as well as by peripheral vasodilation (26). Also, changes in regional perfusion with isoflurane are in general agreement with the effects of inhalation of this drug in humans. Hence, we measured a relative overperfusion of the myocardium (42), renal blood flow decreased slightly (43), and total hepatic blood flow was essentially unchanged from control owing to splanchnic vasodilation (44).

In summary, our results indicate that equipotent hemodynamic concentrations of sevoflurane and isoflurane have very similar effects on the systemic circulation, although isoflurane in high concentrations has a pronounced impact on peripheral resistance and maintains cardiac output at higher levels than does sevoflurane. The effects of both anesthetics on splanchnic and renal blood flows were almost identical, whereas isoflurane was a more potent vasodilator in cerebral and myocardial vascular beds.

References

1. Manohar M, Parks C. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia without and with 50% nitrous oxide. J Pharm Exp Ther 1984;231:640–8.
2. Kazama T, Ikeda K. Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. Anesthesiology 1988;68:435–7.
3. Bernard JM, Wouters PF, Doursout MF, Florence B, Chelly JE, Merin RG. Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Anesthesiology 1990;72:659–62.
4. Scheller MS, Tateishi A, Drummond JC, Zornow MH. The effects of sevoflurane on cerebral blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram are similar to those of isoflurane in the rabbit. Anesthesiology 1988;68:548–51.
5. Heymann MA, Payne BD, Hoffmann JIE, Rudolph AM. Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 1977;20:55–79.
6. Stanek KA, Coleman TG, Smith TL, Murphy WR. Two hemodynamic problems commonly associated with the microsphere technique for measuring regional blood flow in rats. J Pharmacol Methods 1985;13:117–24.
7. Ishise S, Pegram BL, Yamamoto J, Kitamura Y, Frohlich ED. Reference sample microsphere method: cardiac output and blood flows in conscious rats. Am J Physiol 1980;239:H443–9.
8. Biewald N, Billmeier J. Blood volume and extracellular space (ECS) of the whole body and some organs of the rat. Experentia 1978;34:412–3.
9. Gross W, Schosser R, Messmer K. MIC-III—an integrated software package to support experiments using the radioactive microsphere technique. Comput Methods Programs Biomed 1990;33:65–85.
10. Tsuchiya M, Ferrone RA, Walsh GM, Frohlich ED. Regional blood flows measured in conscious rats by combined Fick and microsphere methods. Am J Phyisol 1978;235:H357–60.
11. Buckberg GD, Luck JC, Payne BD, Hoffmann JIE, Archie JP, Fixler DE. Some sources of error in measuring regional blood flow with radioactive microspheres. J Appl Physiol 1971;31: 598–604.
12. Ross WT, Daggy BP. Hepatic blood flow in phenobarbital-pretreated rats during halothane anesthesia and hypoxia. Anesth Analg 1981;60:306–9.
13. Seyde WC, Longnecker DE. Anesthetic influences on regional hemondynamics in normal and hemorrhaged rats. Anesthesiology 1984;61:686–98.
14. White PF, Johnston RR, Eger EI. Determination of anesthetic requirement in rats. Anesthesiology 1974;40:52–7.
15. Cook TL, Beppu WJ, Hitt BA, Kosek JC, Mazze RI. Renal effects and metabolism of sevoflurane in Fisher 344 rats: an in-vivo and in-vitro comparison with methoxyflurane. Anesthesiology 1975;43:70–7.
16. Miller ED, Kistner JR, Epstein RM. Whole-body distribution of radioactively labelled microspheres in the rat during anesthesia with halothane, enflurane, or ketamine. Anesthesiology 1980;52:296–302.
17. Conzen PF, Hobbhahn J, Goetz AE, et al. Splanchnic oxygen consumption and hepatic surface oxygen tensions during isoflurane anesthesia. Anesthesiology 1988;69:643–51.
18. Conzen, PF, Hobbhahn J, Goetz AE, et al. Myocardial contractility, blood flow and oxygen consumption in healthy dogs during anesthesia with isoflurane and enflurane. J Cardiothorac Anesth 1989;3:70–7.
19. Kazama T, Ikeda K. The comparative cardiovascular effects of sevoflurane with halothane and isoflurane. J Anesth 1988;2: 63–8.
20. Kotorly KJ, Ebert TJ, Vucins E. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 1984;60:173–9.
21. Bagshaw RJ, Cox RH. Baroreceptor control of central and regional hemodynamics with isoflurane in the dog. Acta Anaesthesiol Scand 1988;32:82–92.
22. Bosnjak ZJ, Kampine JP. Effects of halothane, enflurane, and isoflurane on the SA-node. Anesthesiology 1983;58:314–9.
23. Manohar M, Parks C. Regional distribution of brain and myocardial perfusion in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia produced without or with 50% nitrous oxide. Cardiovasc Res 1984;18:344–53.
24. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occulusion. Anesthesiology 1987;66:280–92.
25. Habazettl H, Conzen PF, Hobbhahn J, et al. Left ventricular oxygen tensions in dogs during coronary vasodilation by enflurane, isoflurane and dipyridamole. Anesth Analg 1989; 68:286–94.
26. Eger EI. The pharmacology of isoflurance. Br J Anaesth 1984; 56:71S–98S.
27. Hansen TD, Warner DS, Todd MM, Vust LJ, Trawick DC. Distribution of cerebral blood flow during halothane versus isoflurane anesthesia in rats. Anesthesiology 1988;69:332–7.
28. Drummond JC, Todd MM, Scheller MS, Shapiro HM. A comparison of the direct cerebral vasodilating potencies of halothane and isoflurane in the New Zealand white rabbit. Anesthesiology 1986;462–7.
29. Michenfelder JD. The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. Anesthesiology 1974;59:23–8.
30. Todd MM, Drummond JC, Shapiro HM. A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. Anesthesiology 1984;60:276–82.
31. Scheller MS, Todd MM, Drummond JC. Isoflurane, halothane, and regional cerebral blood flow at various levels of $PaCO_2$ in rabbits. Anesthesiology 1986;64:598–604.
32. Eintrei C, Leszniewski W, Carlsson C. Local application of 133 xenon for measurement of regional cerebral blood flow during halothane, enflurane and isoflurane anesthesia in humans. Anesthesiology 1985;63:391–4.
33. Nöldge GFE, Priebe HJ, Kopp KH, Pelchen T, Riegel W, Geiger K. Differences in effects of isoflurane and enflurane on splanchnic oxygenation and hepatic metabolism in the pig. Anesth Analg 1990;71:258–67.
34. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 1984;63: 557–65.
35. Frink EJ, Morgan SE, Coetzee A, Scipione PJ, Brown BR. Effects of sevoflurane, isoflurane and halothane on hepatic

blood flow and oxygenation in chronically instrumented greyhound dogs. Anesthesiology 1990;73:A558.
36. Vollmar B, Kerner T, Vierl M, et al. Blood flow to splanchnic organs and tissue oxygenation of liver and pancreas during enflurane induced hypotension. Anesthesiology 1990;73:A614.
37. Eliassen E, Folkow B, Hilton S. Blood flow and capillary filtration capacities in salivary and pancreatic glands as compared with skeletal muscle. Acta Physiol Scand 1973;87:11A.
38. Jansson L, Sandler S. Pancreatic islet circulation in relation to the diabetogenic action of streptozotocin in the rat. Endocrinology 1985;116:896–900.
39. Jarnberg PO, Marrone B, Priano LL. Enflurane preserves renal blood flow. Anesthesiology 1990;73:A572.
40. Arendshorst WJ, Finn WF, Gottschalk CW. Autoregulation of blood flow in the rat kidney. Am J Physiol 1975;228:127–33.
41. Malik AB, Loegeriz DJ, Saba TM, et al. Cardiac output and regional blood flow following trauma. Circ Shock 1978;5:73–84.
42. Reiz S, Balfors E, Sorensen MB, Ariola S, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59:91–7.
43. Groves ND, Leach KG, Rosen M. Effects of halothane, enflurane and isoflurane anaesthesia on renal plasma flow. Br J Anaesth 1990;65:796–800.
44. Goldfarb G, Debaene B, Ang ET, Roulot D, Jolis P. Lebrec D. Hepatic blood flow in humans during isoflurane-N_2O and halothane-N_2O anesthesia. Anesth Analg 1990;71:349–53.

Halothane- and Enflurane-Induced Inhibition of Phasic Responses to Carbachol in Isolated Guinea Pig Trachea

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Volatile anesthetics produce bronchodilatation by a combination of effects on the autonomic nervous system as well as direct effects on the airway smooth muscle. We sought to further explain the direct effects on airway smooth muscle by studying the effect of volatile anesthetics on the phasic and tonic components of the contractile response. The effects of 1.2%, 2.3%, and 4.3% halothane and 1.6%, 3.2%, 4.9%, and 8.7% enflurane on the phasic and tonic components of the contractile response to 10 μM carbachol and 40 mM KCl in isolated guinea pig trachea were determined using steady-state and kinetic analyses. No direct effect of either anesthetic on resting tension was observed. The peak tensions of the phasic responses to 10 μM carbachol were significantly inhibited by all concentrations of halothane and enflurane. The inhibition by enflurane was concentration-dependent and eliminated the phasic response at 8.7%. The peak tensions of the tonic responses to 10 μM carbachol were unaffected. The peak tensions of the responses to 40 mM KCl were unaffected by halothane but were significantly inhibited by 4.9% enflurane. The decay rate of the phasic response was unaffected by the anesthetics. The onset rate of the tonic response was significantly inhibited only by 8.7% enflurane, whereas halothane was without effect. The EC_{50} concentration for carbachol, as determined by cumulative concentration response curves, was increased by both 8.7% enflurane and 4.3% halothane. The results support the hypothesis that halothane and enflurane inhibit that portion of the contractile response to carbachol dependent on the release of intracellular Ca^{2+}. This effect occurs at anesthetic concentrations that have no apparent effect at the receptor, as suggested by the lack of effect on the EC_{50} for carbachol, and suggests a direct effect on the availability of intracellular Ca^{2+}. In addition, higher concentrations of enflurane appear to inhibit the entry of extracellular Ca^{2+} through voltage-operated channels and receptor-operated channels as well.

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Volatile anesthetics can change the mobilization of intracellular Ca^{2+}. In skinned muscle preparations, isoflurane and halothane can inhibit the release of myocardial sarcoplasmic reticulum Ca^{2+} (1) and, in vascular smooth muscle, halothane can cause both the release of sarcoplasmic reticulum Ca^{2+} and the inhibition of the intracellular Ca^{2+} accumulation (2). In airway smooth muscle (ASM), there is indirect evidence that halothane causes the release of intracellular Ca^{2+} (3).

In many types of smooth muscle including ASM, an agonist-induced contraction consists of an initial rapid phasic component followed by a sustained tonic contracture (4,5). The phasic and tonic components of the response can be isolated by manipulation of the extracellular Ca^{2+} concentration. The phasic component of the response is believed to be due to the transient release of Ca^{2+} from intracellular stores, whereas the tonic component is dependent to a large extent on the influx of extracellular Ca^{2+} (6,7).

To our knowledge, there have not been any studies on the effects of volatile anesthetics on the phasic and tonic components of the contractile response in ASM. The present experiments were performed to study the direct effects of halothane and enflurane in ASM on the phasic and tonic components of the contractile response to a muscarinic receptor agonist (carbachol), and to a depolarizing and receptor-independent spasmogen (KCl). We also analyzed the kinetic variables describing these responses because they have been shown in vascular smooth muscle to provide additional mechanistic information about these responses that is unavailable from the steady-state analysis alone (8,9) and that may help to further explain the manner in which the anesthetics directly

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change the response of ASM to contractile agonists. The experiments were performed in epithelium-free isolated smooth muscle to eliminate the effects of reflex nervous activity, and any possible modulatory effects of the respiratory epithelium (10). We propose that the volatile anesthetics would have a similar effect in ASM as seen in myocardial and vascular tissue and would be manifested as an attenuation of the phasic response.

Methods

The studies were performed in accordance with the guidelines of the institutional Animal Care and Use Committee of the Mount Sinai School of Medicine. Male Albino-Hartley guinea pigs (Charles River, Wilmington, Mass.) were asphyxiated with 100% CO_2 and rapidly exsanguinated. The trachea was rapidly excised, dissected free of connective tissue, and placed in oxygenated Krebs-bicarbonate buffer. The trachea was cut into cylindrical segments approximately eight cartilaginous rings in length, and the luminal surface was scraped with a small brush (Proxibrush refill, Butler) to remove the epithelial cell layer. Histologic examination of the trachea confirmed that the epithelial layer was completely removed without any histologic evidence of damage to the underlying muscle layer.

Two segments from each trachea were suspended between two L-shaped parallel stainless steel hooks and were mounted in 20-mL organ baths at 37°C, containing normal Krebs-bicarbonate buffer (mM: NaCl 124; KCl, 5; $MgSO_4$, 1.3; $CaCl_2$, 2.5; $NaHPO_4$, 0.6; $NaHCO_3$, 25; and glucose, 10 in glass-distilled deionized water). The bath was continuously bubbled with a 95% O_2–5% CO_2 gas mixture to maintain a pH of 7.4. The tissue segments were placed under approximately 10-g tension and equilibrated for 2 h with frequent changes of buffer. During this equilibration period, the tissues relaxed to a steady resting tension (4–6 g). The high initial tension on the trachea allowed for stress relaxation and optimization of the resting length of the muscle (11). One of the L-shaped hooks was anchored to the bottom of the organ bath, and the other was tied to a force displacement transducer (FT03, Grass Instruments Co., Quincy, Mass.) to measure changes in tension isometrically that were then recorded on a Grass polygraph (Grass 7D). Contractile responses were generated by adding a drug directly to the bath. Washout of drugs was achieved by emptying the organ bath and refilling with fresh buffer several times.

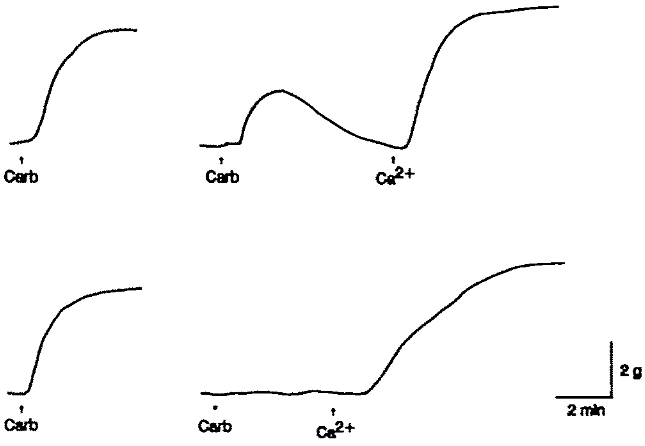

Figure 1. Tracings of original polygraph recordings showing the sequence of generation of the responses to 10 μM carbachol (Carb) in isolated guinea pig trachea. After the initial response to Carb (*upper panel*), the tissues were washed; and after return to a stable baseline tension, the tissues were incubated in Ca^{2+}-depleted buffer for 5 min. Carbachol was then added to generate the phasic response. After the phasic response decayed to the baseline tension, Ca^{2+} was restored to 2.5 mM, which results in the generation of the tonic response. *Lower panel*: 1 h after washout of the first tonic response, the same tracheal segment was incubated in normal buffer equilibrated with 8.7% enflurane. After a 30-min incubation, the sequence of responses was repeated in the presence of anesthetic. Note that enflurane completely inhibited the phasic response and slowed the onset rate of the tonic response but had no effect on the steady-state tension of the tonic response. Drugs were added at the *arrows*.

The sequence of response generation is illustrated in Figure 1. Before each assay, tissue responsiveness was ascertained by assessing the response to 10 μM carbachol in normal Krebs' buffer solution. After washout of this response and a return to a stable resting tension, the tissues were incubated in Ca^{2+}-depleted buffer prepared by omitting the $CaCl_2$ from the normal buffer and by adding 2 mM of the chelating agent EGTA. After 5 min, 10 μM carbachol was added to the bath. The increase in tension to carbachol in Ca^{2+}-depleted, EGTA-containing buffer was phasic in nature and demonstrated a decay back to resting tension. Preliminary testing confirmed that after a 5-min incubation in the Ca^{2+}-depleted buffer, no contraction to KCl is produced as has been previously reported (12). This Ca^{2+}-depleted, EGTA-resistant response is termed the phasic response. After the phasic response had decayed to resting tension, the bath concentration of Ca^{2+} was restored to 2.5 mM by the addition of 90 μL of 1.0 M $CaCl_2$ (calculated to correct for the chelating effect of EGTA and to increase the bath concentration of Ca^{2+} to 2.5 mM). This produced a sustained tonic response. In some experiments, the response to 40 mM KCl was determined between the initial carbachol response and the generation of the phasic and tonic responses. In these experiments, after the initial response to carbachol was determined, the tissues were washed several times with normal Krebs' buffer solution and were allowed to relax to a stable resting tension. The KCl was then added directly to the bath to increase the KCl concentration to 40 mM. After this response reached a steady-state tension, the tissues were washed with normal Krebs' buffer and were allowed to return to a steady resting tension before generation of the phasic and tonic responses.

After a washout of the first tonic response, the tissues were allowed to equilibrate to a stable resting tension with frequent changes of buffer. One hour after washout of the first tonic response, the tissues were incubated in a normal buffer solution previously equilibrated with anesthetic. Both the normal and Ca^{2+}-depleted buffer solutions were previously equilibrated with anesthetic. The solutions were continuously gassed with anesthetic delivered from calibrated vaporizers (Foregger or Ohio Medical Products, Madison, Wis.) at 0.6 L/min using 95% O_2–5% CO_2 as the carrier gas. To deliver 8.7% enflurane, a copper kettle was used. Anesthetic partial pressure in the gas leaving the buffer solution was continuously monitored with an anesthetic agent monitor (Datex, Puritan Bennet). The vaporizers were adjusted to maintain concentrations of 1.6%, 3.2%, 4.9%, or 8.7% enflurane or 1.2%, 2.3%, or 4.3% halothane in the gas phase above the equilibrated buffer solutions. These concentrations were equivalent to 1.2, 2.3, and 4.3 MAC for halothane and 0.83, 1.47, 2.25, and 4.0 MAC for enflurane using the reported guinea pig MAC values of 1.01% for halothane and 2.17% for enflurane (13).

The tissues were equilibrated for 30 min at a constant anesthetic concentration. During this period and throughout the remainder of the experiment, the same anesthetic mixture was bubbled into the individual organ baths. The tissue responsiveness and generation of the KCl, phasic, and tonic responses were determined again in anesthetic-equilibrated buffer solution. Each tracheal segment was exposed to only one anesthetic concentration. One of the two segments from each trachea was used as a time control and was simultaneously treated in an identical manner except that it was not exposed to the anesthetic.

Cumulative concentration response curves were generated in tissues before and after exposure to the anesthetic, as well as in time-matched control tissues. Cumulative concentration response curves were obtained in normal Kreb's buffer solution by the cumulative addition of carbachol to the bath in one-half log increments from 10^{-8} to 10^{-4} M. After the addition of each concentration of carbachol, the response was observed until a steady tension was achieved. The concentration of carbachol was increased by adding more carbachol to the bath until there was no further increase in tension with two successive concentrations of carbachol.

The anesthetic concentrations in the buffer solutions were measured at equilibrium by flame ionization gas chromatography based on the method of Bazil et al. (14). Equilibrated buffer (1 mL) was extracted with 0.5 mL of heptane that contained 1 mM hexane as an internal standard. The extracts were injected (1 μL) onto a 1.83-m-long column with an inside diameter of 2.16 mm packed with 10% Apiezon L on Chromosorb W-HP (80/100). The temperatures of the injector, column, and detector were 120, 60, and 200°C, respectively. The carrier gas was nitrogen at a flow rate of 20 mL/min. The concentrations of halothane were determined to be 0.43, 0.72, and 1.23 mM at 1.2%, 2.3%, and 4.3%, respectively. The concentrations of enflurane were 0.52, 1.04, 1.64 mM at 1.6%, 3.2%, and 4.9%, respectively. The equilibrium concentration for 8.7% enflurane was extrapolated from additional data to be 3.06 mM.

The peak tensions for all responses were measured manually from the original polygraph tracings in which phasic and tonic responses were digitized manually using the Sigma-Scan Measurement System (Jandel Scientific, Corte Madera, Calif.). The curves for the decay rate of the phasic response and the onset rate of the tonic response were best fit by single exponential functions using a linear least-squares fitting procedure (Sigma Scan). No improvement in fit was obtained by increasing the number of exponential terms. Therefore, an estimate of the apparent rate constant of decay of the phasic response (k_{decay}; min^{-1}) was made from a plot of ln (tension at time t) vs time. The apparent onset rate constant of the tonic response (k_{on}; min^{-1}) was determined by plotting ln [(peak tension−tension at time t)/peak tension] vs time (Sigma-Scan). Values for k_{decay} and k_{on} were derived from the slopes of the regression lines (8,9).

The magnitude of the second set of responses in the time-control tissues differed from the first set of control responses. Therefore, the peak tensions of the responses in the presence of anesthetic were expressed as a percentage of the responses before exposure to anesthetic for each individual tissue segment. The anesthetic-exposed groups were compared with the time-control segments by one-way analysis of variance followed by *t*-tests where appropriate. Correction was made for the use of multiple *t*-tests, and *P* values < 0.05 were accepted as significant.

Halothane was obtained from Halocarbon Laboratories, Inc. (Augusta, S.C.) and enflurane from Anaquest (Madison, Wis.). All other drugs and chemicals were supplied by Sigma (St Louis, Mo.). Carbachol was prepared in glass-distilled deionized water on the day of the experiment and kept on ice for the duration of the experiment.

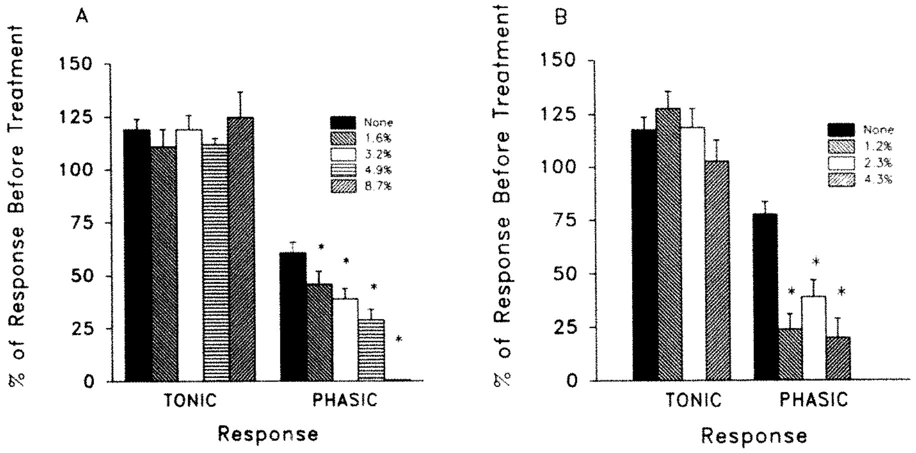

Figure 2. The effects of enflurane (**A**) and halothane (**B**) on the steady-state tensions of the phasic and tonic responses to 10 μM carbachol in isolated guinea pig trachea. Phasic and tonic responses were generated as described in Figure 1 and Methods. The peak tensions of the responses in the presence of anesthetic were expressed as a percentage of the response before exposure to anesthetic for each individual tracheal segment and compared with time-matched control segments from the same tracheas treated identically except that they were not exposed to anesthetic. The number of segments represented by the bars are equal to or greater than the *n*'s for the corresponding groups reported in Table 1. Differences between groups were determined by analysis of variance. The column headed by "None" represents the time-matched control tissues. $^*P < 0.05$.

Results

No changes in resting tension were observed in any tissue segment on exposure to either anesthetic.

The effects of halothane and enflurane on the steady-state contractile responses to carbachol are illustrated in Figures 1 and 2. Analysis of the responses of the time-control tissues indicated that both the phasic and tonic responses were changing with time. The phasic responses to 10 μM carbachol were 61% of the first response in the enflurane group of time-matched tissues and 78% of the first response in the halothane time-matched tissues. The tonic responses increased with time 119% and 118% of the first response for the enflurane and halothane time-matched control tissues, respectively. Accordingly, the response after exposure to anesthetic was expressed as a percent of the control response before exposure to anesthetic and was compared with the time-matched control tissues.

Both halothane and enflurane significantly inhibited the peak tension of the phasic responses to 10 μM carbachol at all concentrations tested (Figures 1 and 2). Enflurane appeared to inhibit the phasic response in a concentration-dependent manner and completely inhibited the response at 8.7%, whereas for halothane, the inhibition appears to be maximal at 1.2%.

The peak tensions of the tonic responses to 10 μM carbachol were unaffected by either anesthetic (Figures 1 and 2). The peak tensions of the responses to 40 mM KCl were unaffected by halothane but inhibited by 4.9% enflurane (73% ± 18%, $n = 6$, for 4.9% enflurane as compared with 132% ± 11%, $n = 12$, for the time-matched controls).

Table 1. Effects of Halothane and Enflurane on the Kinetic Parameters of the Phasic and Tonic Responses to 10 μM Carbachol in Isolated Guinea Pig Trachea

Anesthetic concentration	Calculated rate constants (min^{-1}) k_{decay}	*n*	k_{on}	*n*
Enflurane				
None	0.35 ± 0.03	15	0.42 ± 0.03	24
1.6%	0.29 ± 0.04	7	0.40 ± 0.04	10
3.2%	0.28 ± 0.06	6	0.34 ± 0.06	8
4.9%	0.37 ± 0.05	3	0.32 ± 0.04	9
8.7%	ND	6	0.27 ± 0.03[a]	6
Halothane				
None	0.33 ± 0.04	17	0.72 ± 0.05	12
1.2%	0.33 ± 0.07	5	0.56 ± 0.13	6
2.3%	0.48 ± 0.11	5	0.64 ± 0.08	5
4.3%	0.76 ± 0.32	3	0.50 ± 0.07	6

k_{decay}, apparent decay rate constant of the phasic response; k_{on}, apparent onset rate constant of the tonic response; None, time-matched control tissues; ND, not determined.

Values are mean ± SEM of *n* (number of observations).

[a] $P < 0.05$.

The calculated rate constants for the various responses are shown in Table 1. The k_{decay} of the phasic response and the k_{on} of the tonic response were stable over time. The k_{decay} of the phasic response to 10 μM carbachol was unaffected by either anesthetic (Table 1). As mentioned above, the phasic responses to 10 μM carbachol were completely inhibited by 8.7% enflurane. The k_{on} of the tonic response to carbachol was significantly inhibited only by 8.7% enflurane (Figure 1 and Table 1).

As a reduction in tissue sensitivity to carbachol in the presence of anesthetic might have occurred, cumulative concentration response curves to carbachol in the presence of each anesthetic were determined. Only the highest concentrations of anesthetic tested, 8.7% enflurane and 4.3% halothane, significantly shifted the concentration response curves to the right. Enflurane had the greater effect as indicated by the increase in the EC_{50} concentration for carbachol from 0.24 ± 0.10 μM to 0.9 ± 0.36 μM (mean ± SD, $n = 6$), whereas the shift in the EC_{50} for 4.3% halothane was from 0.26 ± 0.08 μM to 0.40 ± 0.12 μM (mean ± SD, $n = 6$).

Discussion

Airway smooth muscle contraction is composed of both a phasic and tonic component, and the two components of the response can be separated based on their use of different sources of Ca^{2+} to generate a contraction (6). Activation of the muscarinic receptor in smooth muscle leads to the generation of inositol triphosphate (IP_3) and diacylglycerol probably through the intermediate activity of a guanine nucleotide binding protein (G-protein) (15,16). In turn, IP_3 transiently stimulates the release of intracellular Ca^{2+} from the sarcoplasmic reticulum thought to be the source of Ca^{2+} for the phasic response. As IP_3 is rapidly inactivated by a Ca^{2+}-dependent specific phosphatase and as release of intracellular Ca^{2+} is accompanied by the stimulation of Ca^{2+} efflux (17,18), the phasic response decays rapidly. The maintenance of the tonic response is less well understood but depends on the presence of extracellular Ca^{2+} that appears to enter the cell through both voltage- and receptor-operated plasmalemmal Ca^{2+} channels (17,19). It may involve diacylglycerol that can activate protein kinase C (17). Regardless of the source of Ca^{2+}, the contraction is produced by the binding of Ca^{2+} to calmodulin that then binds to the catalytic subunit of myosin light chain kinase. The myosin light chain is then phosphorylated and myosin adenosine triphosphatase is activated by actin (19).

In our experiments, both halothane and enflurane inhibited the phasic response at clinically relevant anesthetic concentrations. The phasic response to 10 μM carbachol appears to be inhibited in a dose-dependent manner by enflurane, whereas the inhibition by halothane appears to reach a maximum at approximately 1.0 MAC with no further increase in inhibition at higher concentrations of halothane. This inhibition of the phasic response may occur from interference at any of a number of steps involved in producing this response.

The phasic response depends on intracellular Ca^{2+} for its generation. Inhibition of the response could result from an anesthetic-related decrease in the amount of Ca^{2+} released from the intracellular Ca^{2+} stores. The effects of volatile anesthetics on Ca^{2+} mobilization have been studied to some extent in myocardium and in vascular smooth muscle. In myocardium, isoflurane and halothane inhibited the release of sarcoplasmic reticulum Ca^{2+} in response to rapid cooling (1). However, although halothane also inhibited the release of sarcoplasmic reticulum Ca^{2+} by rapid depolarization, isoflurane did not (1). In vascular smooth muscle, halothane inhibited the uptake of Ca^{2+} into the sarcoplasmic reticulum and increased the caffeine-induced release of Ca^{2+} from the sarcoplasmic reticulum in permeabilized tissues (2). In canine tracheal muscle, halothane produced a transient contraction in a Ca^{2+}-free, EGTA-containing solution, also suggesting that Ca^{2+} was released from intracellular stores (3). With repeated applications of halothane, this response decayed with time and was restored after incubation in Ca^{2+}-containing buffer solution (3). In other tissues, the effects of volatile anesthetics on intracellular Ca^{2+} have also been variable. In swine hepatocytes, halothane was found to release intracellular Ca^{2+} (20); whereas in a rat pheochromocytoma cell line, halothane, enflurane, and isoflurane had no effect on carbachol-induced release of intracellular Ca^{2+} (21). As mentioned above, the release of intracellular Ca^{2+} by the volatile anesthetics was accompanied by a transient contraction. We did not observe any change in tension with the application of anesthetic. This could be due to species or tissue differences or to methodologic differences in the type of preparation used or the contractile state of the tissues, as other studies have used precontracted tissues. Our results are consistent with an inhibition of uptake of Ca^{2+} into and/or inhibition of its release from the intracellular stores. The lack of effect on the k_{decay} of the phasic response suggests that the mechanisms of free Ca^{2+} removal from the cytoplasm are unaffected by the anesthetics and are not responsible for the inhibition of the phasic response.

The inhibition of the phasic response might also result from an anesthetic-induced decrease in receptor sensitivity to carbachol with a subsequent decrease in the amount of Ca^{2+} released by a given concentration of carbachol. This does not appear to be the case, however, as the EC_{50} concentration of carbachol was only increased by high (4.0 MAC) concentrations of anesthetic whereas the phasic responses were inhibited at lower concentrations. Supporting this lack of effect are data that show little change in the sensitivity to methacholine in intact dogs (22) or the in vitro sensitivity to acetylcholine in canine tracheal muscle (3). Brichant et al. (23) reported small changes in the concentration response curves to acetylcholine in canine tracheal muscle, as did Sayiner et al. (24) for acetylcholine and serotonin, also in canine tracheal muscle. Our data supports an effect beyond the level of the muscarinic receptor. Several studies have reported some inhibition of the contractile proteins themselves by volatile anesthetics (1,2). As the phasic and the tonic responses share the same contractile proteins to generate a response and as the peak tension of the tonic response was unaffected by the anesthetics, a direct effect of the anesthetics on the contractile proteins does not appear to explain the inhibition of the phasic response. Alternatively, as IP_3 formation is a G-protein–dependent process, an anesthetic effect on the G-protein, with a consequent decrease in the amount of IP_3 formed might result in a decrease in the amount of Ca^{2+} released from intracellular stores. Recently it has been demonstrated that several volatile anesthetics can interfere with the receptor-G-protein complex and can inhibit its function (25,26). Thus, an inhibition of the phasic response may be a direct effect of the volatile anesthetics regulating the supply of intracellular Ca^{2+} by inhibiting its release from intracellular stores. The inhibition site could lie at the level of the G-protein.

The tonic component of the response was less affected by the anesthetics. Only the k_{on} of the tonic response to 10 μM carbachol was significantly inhibited and only by 8.7% enflurane. The effect on the k_{on} indicates that the entry rate of extracellular Ca^{2+} is probably slowed by the higher concentrations of anesthetic. The effect on the k_{on} might be explained by an alteration in either voltage- or receptor-mediated Ca^{2+} channels. Korenega et al. (3) demonstrated a hyperpolarization of tracheal smooth muscle at halothane concentrations of 2% or greater. This hyperpolarization might be expected to inhibit the voltage-operated Ca^{2+} channels activated at depolarized potentials. In our experiments, 4.9% enflurane inhibited the response to a depolarizing concentration of KCl. Although this result suggests that at least enflurane is capable of inhibiting voltage-operated Ca^{2+} channels, this inhibiting capability was not reflected in a k_{on} decrease, as k_{on} was not affected by 4.9% enflurane. This suggests that the overall entry rate of Ca^{2+} in response to a muscarinic agonist is not dependent on voltage-operated channels. As receptor-operated Ca^{2+} channels are probably also present in smooth muscle cells (27), these channels might be inhibited by the anesthetics, perhaps through interference with the activation of protein kinase C or by interfering with a G-protein regulated process of channel opening. Kress et al. (21) recently have shown in a rat neuroblastoma cell line that halothane, enflurane, and isoflurane are capable of blocking Ca^{2+} channels that are dihydropyridine-insensitive. However, the significance of the entry rate of Ca^{2+} to the developed steady-state peak tension is not clear. Several recent studies have shown that although increased intracellular Ca^{2+} is related to the developed tension, the degree of myosin light chain phosphorylation and developed tension is greater for a given increase in intracellular Ca^{2+} in the presence of carbachol than when intracellular Ca^{2+} is increased by depolarization with KCl (12,28). This suggests that the ultimate magnitude of the developed tension is not always directly related to the concentration of intracellular Ca^{2+} achieved.

Several limitations of this study should be considered. There were time-dependent changes in both the phasic and tonic responses. Although we cannot explain this change in the preparation, ongoing work suggests that this is not due to the presence of EGTA but may be due to a slow loss in intracellular Ca^{2+} with time. Unpublished data from our laboratory have shown that when tissues are incubated at 25°C, the phasic response does not decrease with time. In addition, the basal tension loss, seen when the tissues are exposed to Ca^{2+}-depleted buffer solution, is greatly reduced at 25°C. This suggests that a loss of intracellular Ca^{2+} is occurring at higher temperatures. The increase in the tension of the tonic response and the KCl response are difficult to explain. Su and Zhang (2) and Brichant et al. (23) have also reported similar time-dependent changes. This does not appear to be due to changes in the sensitivity of the muscarinic receptor with time as the EC_{50} for carbachol did not change with time. An increase in carbachol-stimulated Ca^{2+} influx is also unlikely as the k_{on} of the tonic response did not change with time. It is possible that there was a change in the sensitivity of the contractile proteins to Ca^{2+} with time. As mentioned above, the sensitivity of the contractile proteins to Ca^{2+} appears to be increased by carbachol (12,28). In addition, the intracellular concentration of Ca^{2+} may decrease during a sustained contraction without any change in the developed tension (28). It is possible that prior exposure to carbachol resulted in an increased sensitivity of the contractile proteins to Ca^{2+} and in potentiated subsequent contractile responses.

Another limitation of our study is that the actual Ca^{2+} movements were not measured. However, the relationship of the Ca^{2+} movements to the conditions in which the phasic and tonic responses to carbachol are generated is well established (4–7). Although only suggestive, our results are consistent with the available information on Ca^{2+} mobilization in smooth muscle. Further experiments will be required to confirm these suggestions. In particular, the Ca^{2+} fluxes should be measured simultaneously with the generation of the phasic and tonic responses in ASM. It would also be of interest to determine if other contractile agonists produce similar results.

Although a number of studies have implicated the inhibition of airway reflexes as the mechanism of volatile anesthetic-induced bronchodilatation (22,29), there is also evidence that these drugs can directly affect the ASM (3,30,31). The clinical relevance of these results remains to be elucidated. Our studies were conducted in the trachea and under conditions of isometric tension development. In vivo contraction is not isometric, and the peripheral airways contribute significantly to pulmonary resistance. It is possible that the ASM in the lung periphery may behave differently from the trachea. Differences in the sensitivity to various contractile agonists in different parts of the lung have been reported (32). It is also noteworthy that the innervation of the ASM changes as one proceeds to the lung periphery and in the periphery, direct effects of the anesthetics on the ASM may assume a greater significance than in the more heavily innervated proximal airways.

In the present experiments, we have demonstrated an effect of both halothane and enflurane on a preparation that eliminated the influences of reflex neural activity and of the airway epithelium and suggests that these agents do have some effect on the isolated ASM. The effects appear to involve aspects of the contractile process that use both intracellular and extracellular Ca^{2+} and may be involved in the bronchodilatory effects of the volatile anesthetics.

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References

1. Komai H, Redon D, Rusy BF. Effects of isoflurane and halothane on rapid cooling contractures in myocardial tissue. Am J Physiol 1989;257:H1804–11.
2. Su J, Zhang CC. Intracellular mechanisms of halothane's effect on isolated aortic strips of the rabbit. Anesthesiology 1989;71:409–17.
3. Korenega S, Takeda K, Ito Y. Differential effects of halothane on airway nerves and muscle. Anesthesiology 1984;60:309–18.
4. Bolton TB. Mechanisms of action of transmitters and other substances on smooth muscle. Physiol Rev 1979;59:606–718.
5. Daniel EE, Crankshaw DJ, Kwan C. Intracellular sources of calcium for activation of smooth muscle. In: Kasner S, ed. Trends in autonomic pharmacology. Volume 1. Baltimore: Urban & Schwarzenberg, 1979;443–84.
6. van Breemen C, Aaronson R, Loutzenhiser R, Meisheri K. Calcium fluxes in isolated rabbit aorta and guinea pig tenia coli. Fed Proc 1982;41:2891–7.
7. Hughes AR, Horstman DA, Takemura H, Putney JW Jr. Inositol phosphate metabolism and signal transduction. Am Rev Respir Dis 1990;141:S115–8.
8. Cory RN, Osman R, Maayani S. Kinetic definition of agonist efficacy at a 5-hydroxytryptamine (5HT-2) receptor in isolated rabbit aorta. J Pharmacol Exp Ther 1986;236:48–54.
9. Cory RN, Osman R, Maayani S. Kinetic characterization of the rabbit aorta contractile response to an alpha adrenergic agonist. J Pharmacol Exp Ther 1984;230:162–70.
10. Barnes PJ, Cuss JB, Palmer JB. The effect of airway epithelium on smooth muscle contractility in bovine trachea. Br J Pharmacol 1985;86:685–91.
11. Stephens N. The mechanics of isolated airway smooth muscle. In: Bouhuys A, ed. Airway dynamics: physiology and pharmacology. Springfield: Charles C. Thomas, 1970:191–208.
12. Katsuyama H, Suzuki S, Nishiye E. Actions of second messengers synthesized by various spasmogenic agents and their relation to mechanical responses in dog tracheal smooth muscle. Br J Pharmacol 1990;100:41–8.
13. Seifen AB, Kennedy RH, Bray JP, Seifen E. Estimation of minimum alveolar concentration (MAC) for halothane, enflurane and isoflurane in spontaneously breathing guinea pigs. Lab Anim Sci 1989;39:579–81.
14. Bazil CW, Raux ME, Yudell S, Minneman KP. Equilibration of halothane with brain tissue in vitro: comparison to brain concentrations during anesthesia. J Neurochem 1987;49:952–8.
15. Chilvers ER, Batty IH, Barnes PJ, Nahorski SR. Formation of inositol polyphosphates in airway smooth muscle after muscarinic receptor stimulation. J Pharmacol Exp Ther 1990;252:786–91.
16. Birnbaumer L, Brown AM. G proteins and the mechanism of action of hormones, neurotransmitters and autocrine and paracrine regulatory factors. Am Rev Respir Dis 1990;141:S106–14.
17. van Breemen C, Saida K. Cellular mechanisms regulating $[Ca^{2+}]_i$ smooth muscle. Ann Rev Physiol 1989;51:315–29.
18. Chilvers ER, Nahorski SR. Phosphoinositide metabolism in airway smooth muscle. Am Rev Respir Dis 1990;141:S137–40.
19. Somlyo AP, Himpens B. Cell calcium and its regulation in smooth muscle. FASEB J 1989;3:2266–76.
20. Iaizzo PA, Seewald MJ, Olsen R, et al. Enhanced mobilization of intracellular Ca^{2+} induced by halothane in hepatocytes isolated from swine susceptible to malignant hyperthermia. Anesthesiology 1991;74:531–8.
21. Kress HG, Müller J, Eisert A, Ulrich G, Tas PW, Koschei K. Effects of volatile anesthetics on cytoplasmic Ca^{2+} signaling and transmitter release in a neural cell line. Anesthesiology 1991;74:309–19.
22. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H. Mechanism of action of inhalational anesthesia on airways. Anesthesiology 1982;56:107–11.
23. Brichant J-F, Gunst SJ, Warner DO, Rehder K. Halothane, enflurane, and isoflurane depress the peripheral vagal motor pathway in isolated canine tracheal smooth muscle. Anesthesiology 1991;74:325–32.
24. Sayiner A, Lorenz RR, Warner DO, Rehder K. Bronchodilatation by halothane is not modulated by airway epithelium. Anesthesiology 1991;75:75–81.
25. Anthony BL, Dennison RL, Aronstam S. Disruption of muscarinic receptor-G protein coupling is a general property of liquid volatile anesthetics. Neurosci Lett 1989;99:191–6.
26. Baumgartner MK, Dennison RL, Narayanan TK, Aronstam RS. Halothane disruption of α_2-adrenergic receptor-mediated inhibition of adenylate cyclase and receptor G-protein coupling in rat brain. Biochem Pharmacol 1990;39:223–5.
27. Wallnöffer A, Cauvin C, Lategan TW, Rüegg UT. Differential blockade of agonist- and depolarization-induced $^{45}Ca^{2+}$ influx in smooth muscle cells. Am J Physiol 1989;257:C607–11.
28. Gerthoffer WT, Murphey KA, Gunst SJ. Aequorin luminescence, myosin phosphorylation, and active stress in tracheal smooth muscle. Am J Physiol 1989;257:C1062–8.

29. Shah MV, Hirshman CA. Mode of action of halothane on histamine-induced airway constriction in dogs with reactive airways. Anesthesiology 1986;65:170–4.
30. Fletcher SW, Flacke W, Alper MH. The actions of general anesthetic agents on tracheal smooth muscle. Anesthesiology 1968;29:517–22.
31. Kochi T, Hagiya M, Mizuguchi T. Effects of enflurane on contractile response of canine trachealis muscle. Anesth Analg 1989;69:60–8.
32. Fujiwara T, Itoh T, Kuriyama H. Regional differences in the mechanical properties of rabbit airway smooth muscle. Br J Pharmacol 1988;94:389–96.

Differential Sensitivity of Diabetic Rat Papillary Muscles to Negative Inotropic Effects of Oxybarbiturates Versus Thiobarbiturates

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The negative inotropic effects of oxybarbiturates and thiobarbiturates were examined in papillary muscles isolated from streptozotocin-induced diabetic rats and in papillary muscles from age-matched control rats. The muscles from diabetic rats exhibited less negative inotropic responses to pentobarbital and secobarbital than the muscles from control rats. Conversely, the negative inotropic responses to thiopental and thiamylal were significantly enhanced in diabetic muscles. Differences in sensitivity to pentobarbital between control and diabetic muscles became less marked by treatment with ouabain or by lowering $[Na^+]_o$. Enhancement of the negative inotropic effect of thiamylal observed in diabetic muscles remained unchanged with these treatments. In both control and diabetic muscles, the negative inotropic effect of pentobarbital was completely reversed by increasing $[Ca^{2+}]_o$, but the effect of thiamylal was only partially reversed. These results suggest a difference in mechanism of action involved in establishment of the negative inotropic effects of oxybarbiturates vs thiobarbiturates. Oxybarbiturates appear to exclusively reduce the influx of extracellular Ca^{2+}, whereas thiobarbiturates appear to affect Ca^{2+} movements at the Ca^{2+} storage sites in addition to the Ca^{2+} influx inhibition.

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Diabetes mellitus has a major impact on cardiac morbidity and mortality, and cardiovascular diseases account for nearly 80% of all deaths in diabetic patients (1). Besides the higher incidence of atherosclerotic coronary disease, several studies indicate myocardial dysfunction in diabetic patients (2–4). Ventricular stiffening has been associated with shortening of left ventricular ejection time (5) in a canine model of diabetes. Reduced left ventricular pressure has been reported in the working heart preparation from diabetic rats (6,7). Further, depressed velocity of shortening and a delayed onset of relaxation have been shown in isolated papillary muscles from diabetic rats (8). The cellular and subcellular causes of this myocardial dysfunction remain unclear at present. Biochemical changes such as depressed myosin Ca^{2+}-adenosine triphosphatase activity (9), diminished Ca^{2+} transport of sarcolemmal membrane (10), and reduced Ca^{2+} binding and uptake by sarcoplasmic reticulum (11,12) may be related to myocardial dysfunction. These changes could ultimately result in alterations in cellular Ca^{2+} handling, thereby causing altered responses to inotropic agents (13,14).

We have previously reported that the negative inotropic effects of halothane, enflurane, and isoflurane are attenuated in papillary muscles obtained from diabetic rats (15). Like volatile anesthetic agents, intravenous anesthetic agents, especially barbiturates, exert a direct cardiodepressive action (16,17). The present study was designed to evaluate the inotropic responses to barbiturates in papillary muscles isolated from streptozotocin-induced diabetic rats. In vascular smooth muscles, effects of oxybarbiturates and thiobarbiturates on vascular tone are quantitatively and qualitatively different (18–20). These barbiturates may influence cardiac contractility through different mechanisms. Therefore, we determined whether the diabetic myocardium responds differently to oxybarbiturates versus thiobarbiturates.

Methods

This study was approved by the Hokkaido University School of Medicine Animal Care and Use Committee. Male Wistar rats, 180–220 g, were anesthetized by diethyl ether and received a single intravenous injec-

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tion of 50 mg/kg of streptozotocin via tail vein (n = 78). Streptozotocin was dissolved in a citrate buffer solution (0.1 M citric acid and 0.2 M sodium phosphate, pH 4.5). Control rats were injected with citrate buffer solution alone (n = 78). All rats were maintained on normal pelleted rat diet and water ad libitum until they were killed. At the time of the experiment, blood samples were collected and serum glucose levels were determined by Rapid Blood Analyzer Super using Uni-Kit (Chugai). All animals injected with streptozotocin became diabetic (serum glucose > 400 mg/dL).

Eight to twelve weeks after treatment with streptozotocin or buffer, rats were anesthetized with diethyl ether. The hearts were rapidly excised from open-chest animals and placed in oxygenated Krebs-Henseleit solution at room temperature. One papillary muscle was carefully dissected from the left ventricle of each heart and then mounted vertically in a water-jacketed bath containing 10 mL of Krebs-Henseleit solution. The composition of Krebs-Henseleit solution was as follows (mM): NaCl 119, $CaCl_2$ 2.5, KCl 4.8, $MgCl_2$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 24.9, and glucose 10.0. The solution in the bath was gassed with 95% O_2–5% CO_2 and kept at a constant temperature of 30 ± 1°C. The muscle was stimulated by square pulses of 0.5-Hz frequency, 5-ms duration, and double-threshold voltage. The pulses were delivered by a pair of spiral platinum electrodes connected to an electric stimulator (Sanei-Sokki 3F46) through an isolation unit (Sanei-Sokki 5361). Isometric tension, under a resting tension of 0.5 g, was recorded with a force transducer (Nihon Kohden TB-612T) and displayed on a pen recorder (Nihon Kohden RJG-3026) through a preamplifier (Nihon Kohden RP-5). The preparations were allowed to stabilize for at least 120 min before any experimental procedure was performed.

The concentration-response curves for the negative inotropic effects of barbiturates were determined in a cumulative manner by the stepwise addition of the barbiturates to the bathing medium. The negative inotropic response to each concentration was allowed to reach a steady level before the next addition was made. The equilibration time for each concentration was usually between 10 and 30 min. Thus, the procedure of establishing a complete concentration-response curve of a certain barbiturate took about 90–180 min. Control experiments showed stable steady-state conditions for 240 min after equilibration. The IC_{50} value, i.e., the concentration of the barbiturates that caused 50% decrease in contractile force, was determined from log-probit plots of the individual response versus concentrations. Each concentration-response curve in a given experiment was obtained from eight preparations for thiopental and 10 preparations for pentobarbital, secobarbital, and thiamylal. Only a single concentration-response curve was obtained in each preparation.

In some experiments, 12 control and 12 diabetic preparations were treated with 30 μM ouabain, and 16 control and 16 diabetic preparations were exposed to low $[Na^+]_o$. Low Na^+ solution ($[Na^+]_o$ = 72 mM) was prepared by replacing NaCl with equimolar sucrose to avoid a change in tonicity of the solution. After each treatment contractile force was allowed to reach a steady-state level. This was obtained within 30 min after treatment. Then, the cumulative concentration-response curves for barbiturates were constructed. For each concentration-response curve, six preparations were used except for the cases with thiamylal in low $[Na^+]_o$, which had 10 preparations.

In a series of experiments carried out to examine the influence of $[Ca^{2+}]_o$ on the negative inotropic responses to barbiturates, $[Ca^{2+}]_o$ was reduced from 2.5 to 0.25 mM. Then, 0.9 mM pentobarbital or 0.3 mM thiamylal was added. These concentrations were selected because they produced a decrease in contractile force of nearly 50% in control papillary muscles at 2.5 mM $[Ca^{2+}]_o$ (see Results). When the steady-state contractile force was reached at 20–30 min after the administration, the calcium concentration-response curves were established by the stepwise addition of $CaCl_2$ to the bathing medium. In these experiments, six preparations of control and diabetic rats were used for each concentration-response curve.

The following drugs were used: pentobarbital sodium (Tanabe, Osaka, Japan), secobarbital sodium (Yoshitomi, Osaka, Japan), thiopental sodium (Tanabe), thiamylal sodium (Yoshitomi), ouabain (Sigma, St. Louis, Mo.), and streptozotocin (Sigma).

All data are presented as mean values ± SEM. Analysis by Student's t-test was performed for unpaired observations. $P < 0.05$ was accepted as indicating a significant difference.

Results

The general features of diabetic and age-matched control animals are summarized in Table 1. All dia-

Table 1. Body Weight, Heart Weight, and Plasma Glucose Levels in Control and Diabetic Rats

	Control	Diabetic	P
Body weight (g)	349 ± 5 (78)	157 ± 3 (78)	<0.001
Heart weight (mg)	757 ± 12 (78)	450 ± 9 (78)	<0.001
Plasma glucose (mg/dL)	178 ± 3 (78)	722 ± 15 (78)	<0.001

Results are expressed as mean ± SEM.
Number of animals is given in parentheses.
Statistical significance was determined by Student's t-test for unpaired data.

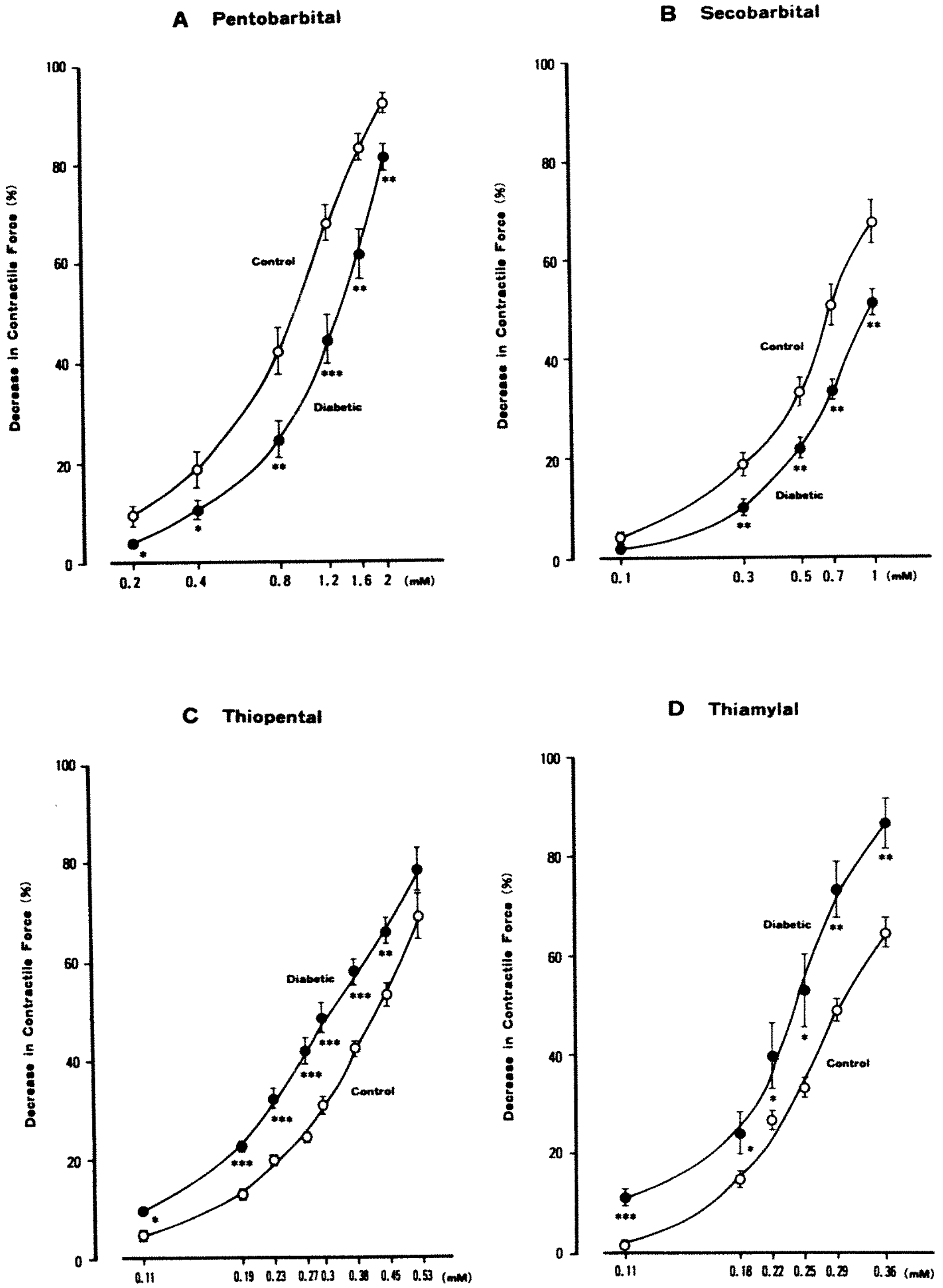

Figure 1. The concentration-response curves for the negative inotropic effects of pentobarbital (**A**), secobarbital (**B**), thiopental (**C**), and thiamylal (**D**) in papillary muscles from diabetic and control rats. Values are expressed as mean ± SEM of eight to 10 preparations. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, compared with the corresponding values in control preparations (unpaired *t*-test).

betic rats were severely hyperglycemic (range 465–1176 mg/dL), and their serum glucose levels were several times higher than that of control animals. Weight gain during the 8–12 wk after treatment with streptozotocin or buffer was significantly less in diabetic animals than in control ones, so that diabetic rats had significantly lower body weight at the time of death. Table 1 also illustrates that heart weights of diabetic rats were significantly lower than that of controls.

Table 2. The IC_{50} Values for the Negative Inotropic Effects of Barbiturates in Papillary Muscles From Control and Diabetic Rats

	IC_{50} (mM)		
	Control	Diabetic	P
Pentobarbital	0.91 ± 0.05 (10)	1.34 ± 0.09 (10)	<0.01
Secobarbital	0.76 ± 0.09 (10)	1.03 ± 0.07 (10)	<0.05
Thiopental	0.43 ± 0.01 (8)	0.32 ± 0.02 (8)	<0.01
Thiamylal	0.30 ± 0.03 (10)	0.24 ± 0.04 (10)	<0.001

Results are expressed as mean ± SEM.
Number of the preparations is given in parentheses.
Statistical significance was determined by Student's t-test for unpaired data.

When the papillary muscles were electrically paced at 0.5 Hz, there was no difference in basal contractile force between the control and diabetic groups. Basal contractile force was 479 ± 27 mg (n = 78) and 452 ± 24 mg (n = 78) for control and diabetic preparations, respectively.

All barbiturates caused concentration-dependent decreases in contractile force in both control and diabetic muscles (Figure 1). The thiobarbiturates thiopental and thiamylal were more potent in producing a negative inotropic effect than the oxybarbiturates pentobarbital and secobarbital in both groups (Table 2). Papillary muscles from diabetic animals exhibited significantly lesser responses to pentobarbital and secobarbital than the corresponding muscles from control rats (Figure 1A and 1B). The IC_{50} values for the oxybarbiturates in the diabetic group were significantly higher in comparison with those in the control group (Table 2). In contrast, negative inotropic effects of thiopental and thiamylal were significantly enhanced in diabetic muscles (Figures 1C and 1D). The IC_{50} values for the thiobarbiturates were significantly lower in the diabetic group (Table 2).

Several lines of evidence have suggested that diabetic myocardium has a propensity for developing intracellular Ca^{2+} overload (13,21). Thus, to investigate the possible role of the Ca^{2+} overload in the altered responses of diabetic myocardium to the barbiturates, the negative inotropic effects of pentobarbital and thiamylal were examined in control and diabetic papillary muscles under the experimental conditions that can produce the Ca^{2+} load: pretreatment with ouabain or decrease in $[Na^+]_o$. In control preparations, ouabain (30 μM) and low $[Na^+]_o$

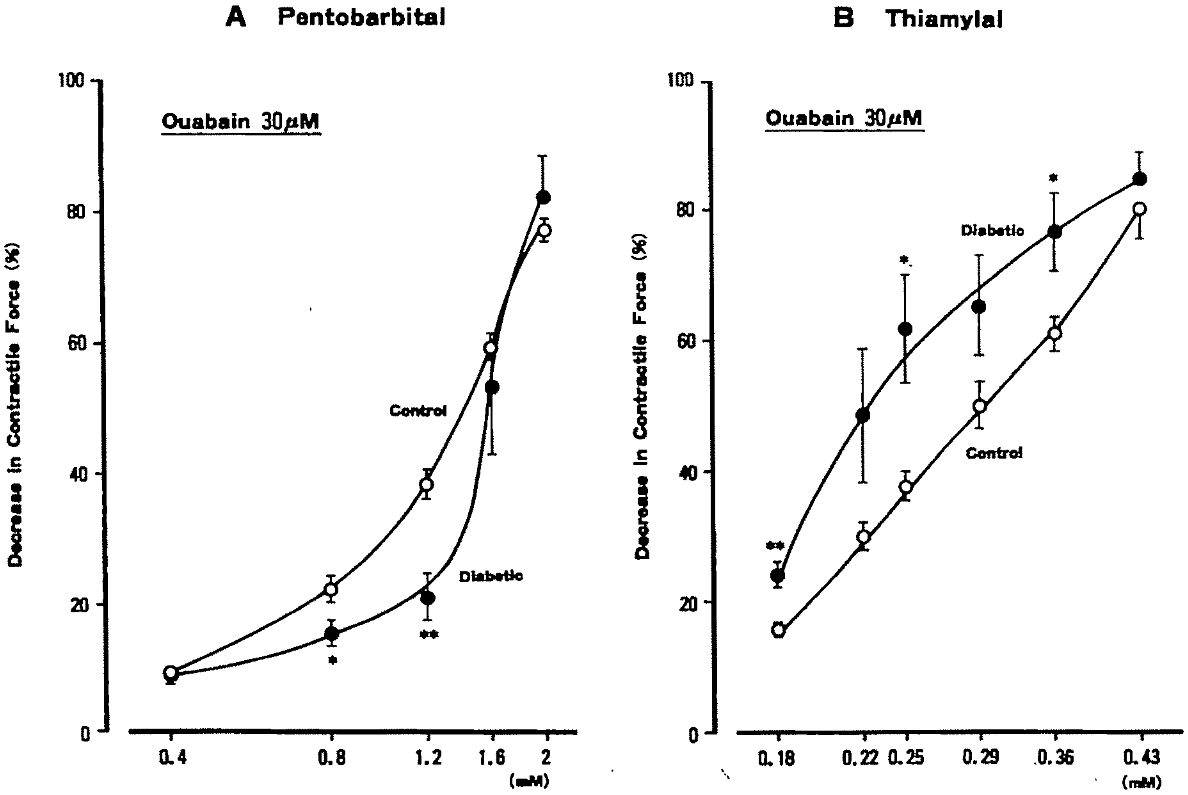

Figure 2. Influence of ouabain on the negative inotropic effects of pentobarbital (A) and thiamylal (B) in papillary muscles from diabetic and control rats. The preparations were treated with ouabain at a concentration of 30 μM. When a steady-state level of contractile force was reached, the barbiturates were applied. Values are expressed as mean ± SEM of six preparations. $^*P < 0.05$, $^{**}P < 0.01$, compared with the corresponding values in control preparations (unpaired t-test).

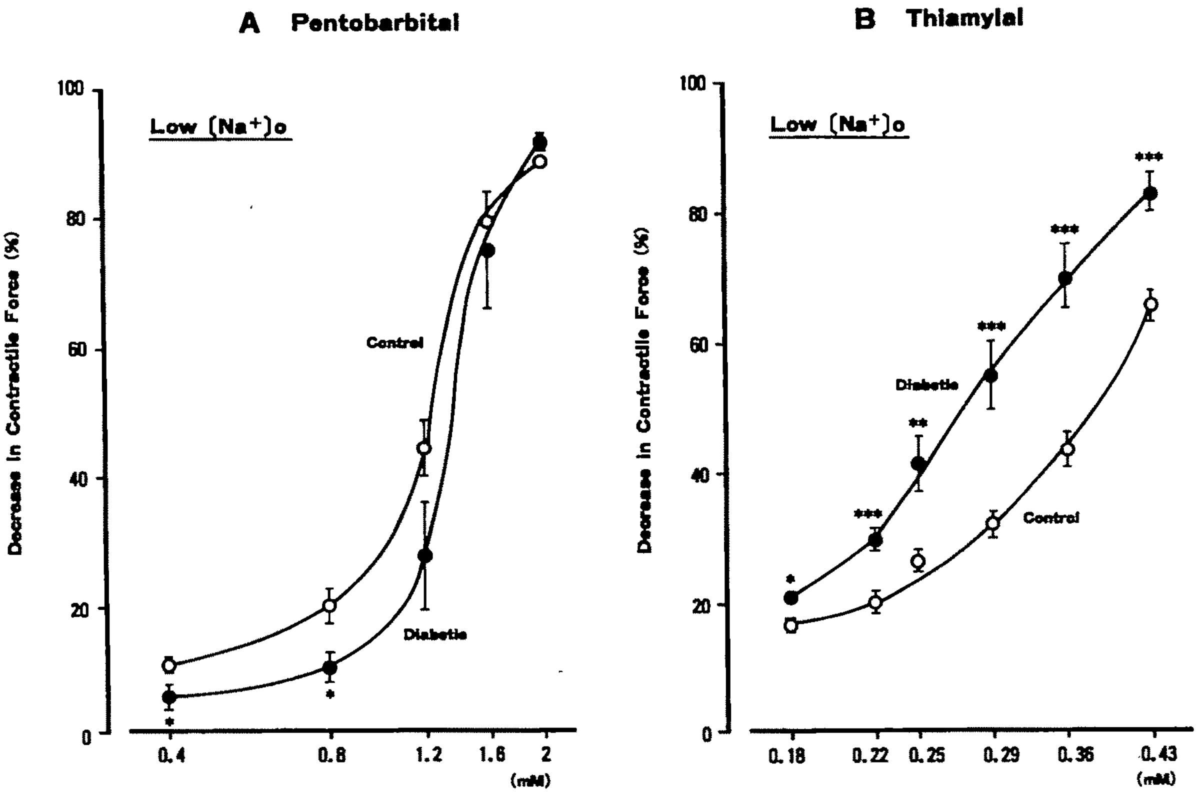

Figure 3. Influence of low $[Na^+]_o$ on the negative inotropic effects of pentobarbital (A) and thiamylal (B) in papillary muscles from diabetic and control rats. The preparations were treated with low Na^+ solution ($[Na^+]_o$ = 72 mM), which was prepared by replacing NaCl with equimolar sucrose. When a steady-state level of contractile force was reached, the barbiturates were applied. Values are expressed as mean ± SEM of six to 10 preparations. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, compared with the corresponding values in control preparations (unpaired *t*-test).

(72 mM) increased contractile force to 113% ± 4% (n = 12) and to 113% ± 9% (n = 16) of basal force, respectively. In contrast, in diabetic preparations, ouabain and low $[Na^+]_o$ failed to produce an increase in contractile force; the corresponding changes in contractile force were 96% ± 4% (n = 12) and 98% ± 5% (n = 16) of basal force, respectively. In the presence of ouabain, the difference between control and diabetic muscles in the negative inotropic response to pentobarbital became obscure (Figure 2A). The IC_{50} values for pentobarbital obtained in the presence of ouabain were not significantly different between control and diabetic muscles (1.42 ± 0.04 mM vs 1.34 ± 0.09 mM, n = 6 for each group). Thus, in control muscles, the IC_{50} value with ouabain treatment was significantly greater than the untreated value (see Table 2). These results imply that pretreatment with ouabain decreased sensitivity of control muscles to pentobarbital to the level of the diabetic muscles without ouabain treatment. As shown in Figure 3A, similar patterns were seen with low $[Na^+]_o$ in that the IC_{50} values were 1.25 ± 0.05 mM (n = 6) in control muscles and 1.39 ± 0.08 mM (n = 6) in diabetic muscles, and the difference between these values was not significant. These IC_{50} values were very close to the corresponding value of diabetic muscles without treatment (see Table 2). On the other hand, even in the presence of ouabain or low $[Na^+]_o$, diabetic papillary muscles were more sensitive to the negative inotropic action of thiamylal than control ones (Figures 2B and 3B). For instance, the IC_{50} values for thiamylal when ouabain was present were 0.30 ± 0.01 mM (n = 6) in control muscles and 0.24 ± 0.01 mM (n = 6) in diabetic muscles, and the difference between these two values was statistically significant ($P < 0.01$). In addition, these IC_{50} values were comparable to the corresponding values obtained in the absence of ouabain (see Table 2).

The influence of $[Ca^{2+}]_o$ on the negative inotropic effects of pentobarbital and thiamylal is shown in Figure 4. In the presence of 0.9 mM pentobarbital, the levels of contractile force in diabetic muscles significantly exceeded control values when $[Ca^{2+}]_o$ was increased from 0.5 to 1.25, 2.5, and 3.75 mM. In other words, the negative inotropic effect of pentobarbital was counteracted by increasing $[Ca^{2+}]_o$ more easily in diabetes than in control. In both groups, the sup-

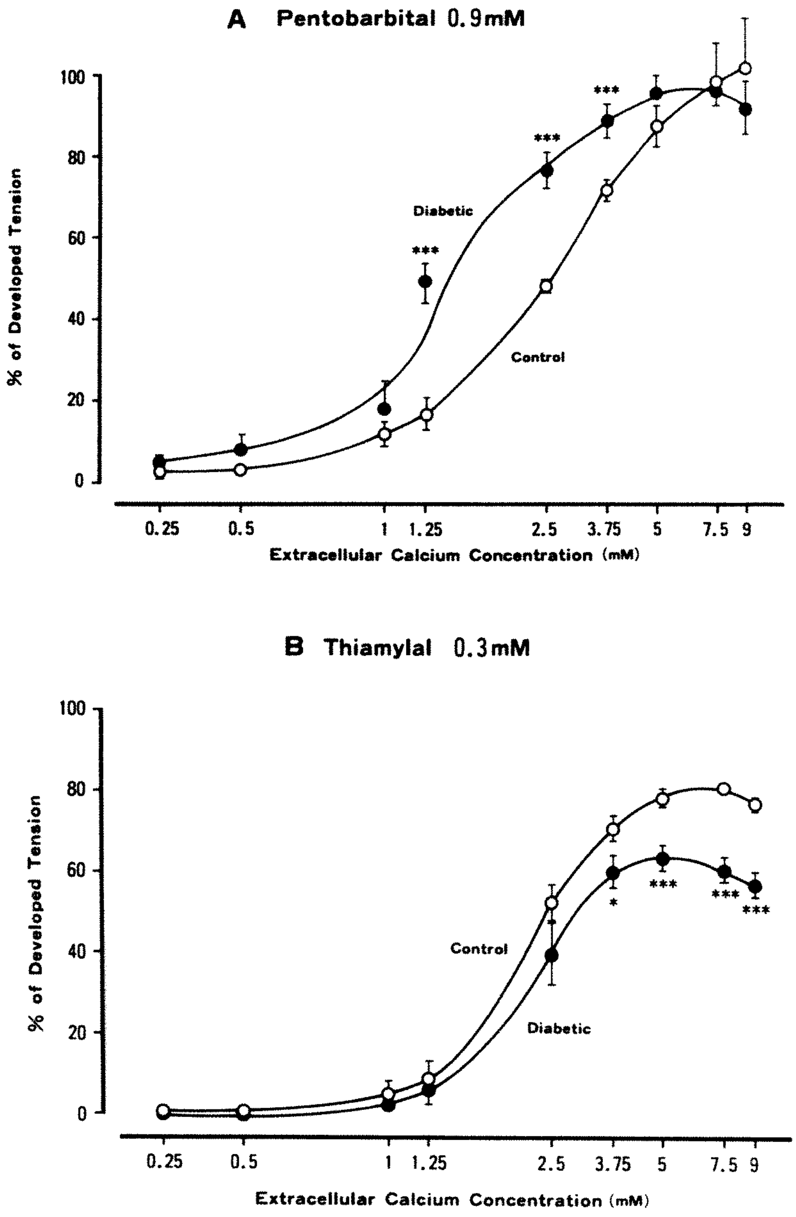

Figure 4. Effect of increasing $[Ca^{2+}]_o$ on the decrease in contractile force induced by 0.9 mM pentobarbital (**A**) and 0.3 mM thiamylal (**B**) in papillary muscles from diabetic and control rats. After the barbiturates produced a stable negative inotropic effect at 0.25 mM $[Ca^{2+}]_o$, the calcium concentration-response curves were determined by the stepwise addition of $CaCl_2$. Basal contractile force at 2.5 mM $[Ca^{2+}]_o$ was taken as 100%. Values are expressed as mean ± SEM of six preparations. $^*P < 0.05$, $^{***}P < 0.001$, compared with the corresponding values in control preparations (unpaired *t*-test).

pressed contractile force by the barbiturate was completely reversed at a $[Ca^{2+}]_o$ of 7.5 mM and higher. In contrast, in the presence of 0.3 mM thiamylal, even raising $[Ca^{2+}]_o$ up to 9 mM failed to produce a complete restoration of contractile force in either group. When thiamylal was present, the contractile force was significantly lower in diabetic muscles than in control ones at higher $[Ca^{2+}]_o$.

Discussion

This study examined the negative inotropic effects of oxybarbiturates and thiobarbiturates on papillary muscles isolated from streptozotocin-induced diabetic rats and from age-matched control rats. The negative inotropic effects of the oxybarbiturates pentobarbital and secobarbital were significantly attenuated in diabetic muscles compared with controls. Conversely, the negative inotropic effects of the thiobarbiturates thiopental and thiamylal were significantly worsened in diabetic muscles.

The data with oxybarbiturates are in agreement with our previous results showing that the negative inotropic effects of volatile anesthetics such as halothane are significantly less in diabetic papillary muscles than in control ones (15). Voltage-clamp studies in mammalian ventricular myocytes have demonstrated that pentobarbital as well as halothane reduces the inward Ca^{2+} current (22,23). Further, reduction in Ca^{2+} entry by pentobarbital into stimulated dog papillary muscle has been shown by Nayler and Merrillees (24) in the staircase method and measurement of $^{45}Ca^{2+}$ influx. We also found that the negative inotropic effect of pentobarbital was reversed by increasing $[Ca^{2+}]_o$. Thus, it seems likely that the negative inotropic effects of oxybarbiturates are mainly due to inhibition of transsarcolemmal Ca^{2+} influx. Because action potentials of diabetic ventricular myocardium are consistently and significantly longer than those of normal ventricular myocardium (13), the prolonged action potential duration might counteract the inhibition of Ca^{2+} influx exerted by oxybarbiturates. This might explain the lowered sensitivity of diabetic muscles to the negative inotropic actions of oxybarbiturates. We favor an alternative explanation, namely that diabetic myocardium has a propensity for developing intracellular Ca^{2+} overload (13,21), which results in counteracting the negative inotropic effects of oxybarbiturates. Support for such a speculation is provided by the finding that, when the Ca^{2+} load can be produced by adding ouabain or by decreasing $[Na^+]_o$, the negative inotropic effect of pentobarbital in control muscles was attenuated to the same extent as diabetic muscles observed under normal conditions. Hence, it is suggested that the less sensitivity of diabetic muscles to oxybarbiturates may be due to impaired regulation of intracellular Ca^{2+} levels in diabetic myocardium.

As with oxybarbiturates, thiobarbiturates are known to reduce the inward Ca^{2+} current in cardiac muscle cells (22,25). However, in contrast to oxybarbiturates, thiobarbiturates resulted in greater negative inotropism in diabetic muscles compared with controls. We also found in both control and diabetic muscles that increased $[Ca^{2+}]_o$ only partially reversed the negative inotropic effect of thiamylal, whereas it completely reversed the effect of pentobarbital. These findings imply that the negative inotropic actions of thiobarbiturates are not simply due to an inhibition of transsarcolemmal Ca^{2+} influx. Thiobarbiturates were more potent in producing a negative inotropic effect than oxybarbiturates even in control muscles, suggesting that the negative inotropic activity is dependent on a function of the structure of barbiturates. Thiobarbiturates are more lipid-soluble than oxybarbiturates because the electronegativity of sulfur is nearly that of carbon (26). Thus, thiobarbiturates would be highly permeable into the cell and might alter the availability of intracellular Ca^{2+} that contributes to contractile activation. Although thiopental is reported not to alter Ca^{2+} uptake by cardiac sarcoplasmic reticulum (27), Komai and Rusy (28) have suggested that thiopental slows the transport of intracellular Ca^{2+} from the site of uptake to the site of release within sarcoplasmic reticulum without much effect on intracellular Ca^{2+}. In fact, the present study showed that the negative inotropic effect of thiamylal remained unchanged by conditions that caused myoplasmic Ca^{2+} overload. It is not clear from the present study what features of the myocardium of diabetic rats result in the enhanced response to thiobarbiturates. Calcium binding and uptake by sarcoplasmic reticulum from hearts of diabetic rats is known to be decreased (11,12). This suggests that thiobarbiturates may interfere more effectively with movement of Ca^{2+} within sarcoplasmic reticulum from the uptake site to the release site, because of the diminished ability of sarcoplasmic reticulum in diabetic myocardium to absorb Ca^{2+}.

In summary, the present study compared the contractile responses of control and diabetic rat papillary muscles to barbiturates. In diabetic muscles, the negative inotropic effects of oxybarbiturates are attenuated, whereas the negative inotropic effects of thiobarbiturates are enhanced. The results provide evidence for differences in mechanisms underlying the negative inotropic action of oxybarbiturates and thiobarbiturates.

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References

1. Kessler I. Mortality experience of diabetic patients. Am J Med 1971;51:715–7.
2. Hamby RI, Zoneraich S, Sherman L. Diabetic cardiomyopathy. JAMA 1974;229:1749–54.
3. Ledet T, Neubauer B, Christensen NJ, Lundback K. Diabetic cardiopathy. Diabetologia 1979;16:207–9.
4. Shapiro LM. Specific heart disease in diabetes mellitus. Br Med J 1982;284:141–1.
5. Regan TJ, Ettinger PO, Khan MI, et al. Altered myocardial function and metabolism in chronic diabetes mellitus without ischemia in dogs. Circ Res 1974;35:222–37.
6. Miller JB Jr. Cardiac performance of isolated hearts of alloxan diabetic rats. Am J Physiol 1979;236:H808–12.
7. Ingebretsen C, Moreau P, Hawelu-Johnson C, Ingebretsen WR. Performance of diabetic rat hearts: effects of anoxia and increased work. Am J Physiol 1980;239:H614–20.
8. Fein FS, Kornstein LB, Strobeck JE, Cappasso JM, Sonnenblick EH. Altered myocardial mechanics in diabetic rats. Circ Res 1980;47:922–33.
9. Malhotra A, Penpargkul S, Fein FS, Sonnenblick EH, Scheuer J. The effect of streptozotocin-induced diabetes in rats on cardiac contractile proteins. Circ Res 1981;49:1243–50.
10. Pierce GN, Kutryk MJB, Dhalla NS. Alterations in Ca^{2+} binding by and composition of the cardiac sarcolemmal membrane in chronic diabetes. Proc Natl Acad Sci USA 1983;80:5412–6.
11. Penpargkul S, Fein FS, Sonnenblick EH, Scheuer J. Depressed cardiac sarcoplasmic reticular function from diabetic rats. J Mol Cell Cardiol 1980;13:303–9.
12. Lopaschuk GD, Tahiliani AG, Vadlamudi RVSV, Katz S, McNeill JH. Cardiac sarcoplasmic reticulum function in insulin- or carnitine-treated diabetic rats. Am J Physiol 1983;245: H969–76.
13. Fein FS, Aronson RS, Nordin C, Miller-Green B, Sonnenblick EH. Altered myocardial response to ouabain in diabetic rats:

mechanics and electrophysiology. J Mol Cell Cardiol 1983;15: 769–84.

14. Horackova M, Murphy MG. Effects of chronic diabetes mellitus on the electrical and contractile activities, $^{45}Ca^{2+}$ transport, fatty acid profiles and ultrastructure of isolated rat ventricular myocytes. Pflügers Arch 1988;411:564–72.
15. Hattori Y, Azuma M, Gotoh Y, Kanno M. Negative inotropic effects of halothane, enflurane, and isoflurane in papillary muscles from diabetic rats. Anesth Analg 1987;66:23–8.
16. Daniel EE, Johnson PK, Foulks JG. The mechanism of the effects of sodium pentobarbital and norepinephrine on isolated cardiac muscle. Arch Int Pharmacodyn Ther 1962;138:276–301.
17. Iwatsuki N. The effects of thiamylal and propanidid on the isolated heart muscle in comparison with CT 1341. Tohoku J Exp Med 1973;110:33–40.
18. Price ML, Price HL. Effects of general anesthetics on contractile responses of rabbit aortic strips. Anesthesiology 1962;23:16–20.
19. Altura BT, Altura BM. Barbiturates and aortic and venous smooth muscle function. Anesthesiology 1975;43:432–44.
20. Hatano Y, Nakamura K, Moriyama S, Mori K, Toda N. The contractile responses of isolated dog cerebral and extracerebral arteries to oxybarbiturates and thiobarbiturates. Anesthesiology 1989;71:80–6.
21. Nordin C, Gilat E, Aronson RS. Delayed afterdepolarization and triggered activity in ventricular muscle from rats with streptozotocin-induced diabetes. Circ Res 1985;57:28–34.
22. Ikemoto Y, Yatani A, Arimura H, Yoshitake J. Reduction of the slow inward current of isolated rat ventricular cells by thiamylal and halothane. Acta Anaesthesiol Scand 1985;29:583–6.
23. Gilat E, Rubinstein I, Binah O. Effect of sodium pentobarbital on the transmembrane action potential and the slow inward current of guinea pig ventricular myocytes. J Cardiovasc Pharmacol 1987;10:485–8.
24. Nayler WG, Merrillees NCR. Cellular exchange of calcium. In: Harris P, Opie LH, eds. Calcium and the heart. London: Academic, 1971:24–65.
25. Ikemoto Y. Reduction by thiopental of the slow-channel-mediated action potential of canine papillary muscle. Pflügers Arch 1977;372:285–6.
26. Harvey SC. Hypnotics and sedatives. The barbiturates. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. New York: Macmillan, 1975:102–23.
27. Blanck TJJ, Stevenson RL. Thiopental does not alter Ca^{2+} uptake by cardiac sarcoplasmic reticulum. Anesth Analg 1988; 67:346–8.
28. Komai H, Rusy BF. Differences in the myocardial depressant action of thiopental and halothane. Anesth Analg 1984;63: 313–8.

Is Resting Membrane Potential a Possible Indicator of Viability of Muscle Bundles Used in the In Vitro Caffeine Contracture Test?

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In 22 patients susceptible to and 34 patients not susceptible to malignant hyperthermia, we examined which muscle conditions may influence the degree of sensitivity of skeletal muscle to the in vitro caffeine contracture test: predrug resting membrane potential, predrug twitch tension, and maximum contracture induced by 32 mM caffeine in two caffeine tests performed respectively at 30 and 75 min after biopsy. No differences in the measured variables were observed between the first and the second caffeine tests in the 34 patients susceptible to malignant hyperthermia. The first caffeine test was found to be positive in all of the 22 patients susceptible to malignant hyperthermia. However, in eight patients, the second caffeine test was negative and the muscle fibers were found to be significantly depolarized. Resting membrane potential was −73.4 ± 7.9 mV before the first caffeine test and −65.8 ± 8.8 mV before the second test. We suggest that when time-induced partial depolarization of malignant hyperthermia–susceptible fibers occurs, fibers may become less sensitive to caffeine.

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The in vitro caffeine contracture test and the in vitro halothane contracture test are the most reliable and specific indicators of malignant hyperthermia susceptibility (MHS) (1,2). Low concentrations of caffeine (i.e., <2 mM) induce contracture in skeletal muscle in humans susceptible to malignant hyperthermia. In malignant hyperthermia–nonsusceptible (MHN) muscle, caffeine-induced contractures are elicited at higher concentrations of caffeine as compared with susceptible (MHS) muscle (1,2).

Malignant hyperthermia investigation units (3–6) are currently investigating which variables may influence the diagnosis of susceptibility to malignant hyperthermia using standard diagnostic protocols (1,2). In the European protocol, a minimum of two muscle strips are tested with halothane and caffeine, respectively. However, the caffeine tests and the halothane tests can be performed either simultaneously or successively. Recently, we observed that, sometimes, in the first of the two successive in vitro caffeine tests, performed contractures developed at lower concentrations of caffeine in MHS muscle than in the second test. Hence, the correlation between two successive caffeine tests becomes sufficiently poor that a patient may be labeled at risk by the criteria of the first caffeine test and not at risk by the criteria of the second. Furthermore, variations of resting membrane potentials from cut human muscle fibers are time-dependent (7). We, therefore, investigated a possible link between those variations and the shift in the caffeine threshold of some tests performed later. We thus tested the sensitivity to caffeine of both MHS and MHN muscle bundles at two different times after biopsy with a new putative appreciation of the state of muscle bundles: predrug resting membrane potential recorded at 30 and 75 min after biopsy. This variable was then compared with two measurable factors generally postulated as being possible indicators of the good quality of muscle fibers: predrug twitch tension and maximum contracture induced by 32 mM caffeine.

Methods

Fifty-six patients admitted for a diagnostic muscle biopsy as part of investigation for malignant hyper-

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thermia participated in the study. The study protocol was approved by the Ethical Committee of the Lille Hospital, but informed consent was not obtained as no extra muscle was removed.

The biopsy specimens were obtained from the vastus lateralis muscle under combined blockade of the femoral nerve and lateral cutaneous nerve of the thigh using lidocaine. The biopsy consisted of one large muscle preparation (30 × 10 mm) from which several muscle strips (18 ± 2 mm long and 2 mm in diameter) were carefully dissected. The fibers were randomly assigned for time to be tested. Thus, it was not possible to choose the quality of muscle strips for the first or second test. One end of the muscle strip was pinned to the silicone bottom of the tissue bath, which was perfused continuously (4–5 mL/min) with Krebs-Ringer solution at 37°C. The Krebs-Ringer solution was of the following composition (mM): NaCl 118.1, KCl 3.4, $CaCl_2$ 2.5, $MgSO_4$ 0.8, KH_2PO_4 1.2, $NaHCO_3$ 25, and glucose 11.1. The pH was 7.35 ± 0.05 and the solution was bubbled with preheated 5% carbon dioxide in oxygen. The other end of the strip was attached by a thin silk thread to a force transducer. The preparations were stimulated directly using silver electrodes with rectangular current pulses of 1-ms duration delivered at a frequency of 0.2 Hz by a stimulator CEA-DAM model GP1-GE2198. The optimal length was determined by increasing the voltage to supramaximal twitch tension and then increasing the length to achieve absolute twitch tension. Baseline and twitch tension were continuously recorded at low speed on a C 1013 Siemens polygraph.

Caffeine contracture test. Pure caffeine was added to the Krebs-Ringer solution in increasing concentrations of 0.5, 1, 1.5, 2, 3, 4, 8, 16, and 32 mM. Each successive concentration of caffeine was administered for 3 min or, in the case of a contracture, until the maximum plateau was reached. Each caffeine test was performed in duplicate at 30 and 75 min after biopsy, and the test giving the greatest increase in tension was used to make the diagnosis.

Halothane contracture test. Halothane was mixed with carbon dioxide in oxygen by means of a calibrated vaporizer (Fluotec Mark III) in concentrations of 0.5%, 1%, 2%, and 3% as measured by gas chromatography corresponding to 0.098 ± 0.010, 0.208 ± 0.021, 0.522 ± 0.040, and 0.710 ± 0.052 mM, respectively. Two halothane tests were performed, and the test giving the greatest increase in tension was used to make the diagnosis.

The criteria of MHS are an increase in resting tension of at least 0.2 g at 2 mM caffeine or less and at 2% halothane or less. A normal response (MHN) was defined as a halothane threshold >2% and a caffeine threshold >2 mM. Other results (i.e., one abnormal response with either halothane or caffeine) were classified equivocal. Halothane and caffeine effects were always tested on separate strips. All experiments were conducted with caffeine. The halothane test was only performed to establish the diagnosis of MHS. Before performing each caffeine test, resting membrane potentials were recorded using conventional glass microelectrodes filled with 3 M KCl and having a tip resistance of 2–5 MΩ connected to the input of a Biologic VF 102 dual microprobe system. Values for membrane potentials were accepted only if, upon impalement, there was a sudden drop in potential that remained constant. At least 15 superficial cells were included in each set of measurements. Resting membrane potentials were recorded across the width of the bundle starting from the middle to ensure that cells were sampled only once.

The amplitude of predrug twitch tension was measured after 15 min of isometric relaxation, just before performing each caffeine test. At the end of the contracture tests, the dimensions of the muscle were measured. The weight of the muscle was determined after cutting the muscle ends off within the silk ties. The average cross-sectional area of the muscle strip was calculated. Maximum 32 mM caffeine-induced contractures were expressed as grams per square centimeter to allow comparison of tension produced by muscle of different cross-sectional areas.

Statistical analysis was performed using a Student's paired *t*-test within groups of either MHS or MHN patients and using a Student's unpaired *t*-test between groups of MHS and MHN patients. Because membrane potentials of several fibers were measured in each of the muscle bundles in the study, data were summarized and compared as follows. Means and standard deviations of resting membrane potentials of a given muscle bundle were obtained using all the measurements available. Statistical analysis was then done using Student's paired or unpaired *t*-test where the consecutive measurements of membrane potential within a muscle bundle were first averaged so that a single measurement for that muscle bundle could be obtained. A *P* value <0.05 was considered significant.

Results

In Vitro Discrimination of Malignant Hyperthermia Susceptibility

A 2 mM caffeine contracture of 0.33 ± 0.25 g developed in muscle bundles from 22 patients at the first caffeine test (30 min after biopsy), and a contracture of 0.56 ± 0.12 g developed at the first static halothane

Table 1. Time-Dependent Changes in Muscle Bundles From 22 Malignant Hyperthermia–Susceptible Patients[a]

	30 Min after biopsy[b]				75 Min after biopsy[c]			
Patient No.	2 mM caffeine (g)	Resting potential (mV)	Twitch tension (g)	32 mM caffeine (g/cm²)	2 mM caffeine (g)	Resting potential (mV)	Twitch tension (g)	32 mM caffeine (g/cm²)
Group 1								
1	0.20	−68.5 ± 6.1 (16)	1.00	45	0.20	−76.0 ± 6.0 (15)	0.80	37
2	0.25	−66.9 ± 5.3 (15)	1.25	33	0.25	−72.8 ± 6.6 (13)	0.95	29
3	0.20	−70.5 ± 8.4 (17)	1.65	31	0.25	−69.5 ± 7.0 (14)	0.84	16
4	0.20	−74.5 ± 5.6 (15)	4.00	43	0.2	−74.0 ± 6.2 (15)	3.80	92
5	0.20	−68.9 ± 2.0 (15)	2.10	33	0.4	−69.2 ± 5.3 (15)	1.60	36
6	0.30	−75.3 ± 4.0 (15)	2.00	64	0.2	−85.8 ± 4.1 (12)	2.10	80
7	0.40	−69.9 ± 2.8 (15)	2.07	56	0.5	−71.4 ± 2.9 (15)	0.92	42
8	0.20	−71.2 ± 3.7 (15)	4.60	25	0.2	−77.0 ± 2.5 (15)	1.16	26
9	0.20	−77.7 ± 7.8 (15)	2.50	41	0.2	−79.1 ± 8.9 (15)	2.20	37
10	0.20	−79.2 ± 4.1 (16)	1.00	37	0.20	−79.0 ± 7.8 (16)	1.02	32
11	0.40	−84.2 ± 3.6 (17)	3.50	33	0.60	−84.4 ± 4.4 (15)	1.80	41
12	0.80	−77.5 ± 5.4 (15)	2.00	90	1.00	−85.0 ± 4.6 (15)	2.50	140
13	1.00	−80.0 ± 4.5 (16)	1.80	70	1.20	−82.0 ± 5.3 (16)	1.70	1.6
14	0.20	−87.6 ± 3.7 (16)	3.50	130	0.20	−88.0 ± 4.0 (15)	3.50	153
Mean	0.33	−75.1	2.35	52.2	0.40	−78.0	1.77	61.9
± SD	0.25	6.2	1.12	28.7	0.32	6.2	0.96	44.4
Group 2								
1	0.27	−61.7 ± 7.4 (12)	0.70	30	0	−56.7 ± 5.3 (9)	0.40	10
2	0.20	−69.1 ± 8.4 (16)	0.60	9	0	−52.6 ± 7.6 (13)	0.30	23
3	0.20	−69.4 ± 7.5 (16)	0.90	48	0	−64.7 ± 4.9 (14)	0.50	15
4	0.20	−70.0 ± 7.5 (16)	0.95	46	0	−65.0 ± 7.6 (14)	0.40	30
5	0.20	−72.0 ± 6.1 (16)	0.70	33	0	−62.0 ± 6.9 (15)	0.65	29
6	0.20	−80.2 ± 4.2 (15)	2.50	67.5	0	−74.2 ± 6.9 (15)	0.90	34
7	0.20	−78.4 ± 3.5 (15)	2.50	25	0	−72.8 ± 5.2 (15)	1.50	40
8	0.30	−87.1 ± 2.7 (16)	3.50	103	0.05	−78.5 ± 6.1 (15)	2.30	100
Mean	0.22	−73.4	1.54	45.1	0.00[d]	−65.8[d]	0.86[d]	35.1
± SD	0.04	7.9	1.11	29.1	0.01	8.8	0.69	27.9

Values for resting potential represent mean ± SD for each patient. Numbers of values are given in parentheses.

[a] *Top*: data from 14 patients with two positive caffeine tests; *bottom*: data from eight patients with the first caffeine test positive and the second negative.

[b] Thirty minutes after biopsy corresponds to the beginning of the first caffeine test.

[c] Seventy-five minutes after biopsy corresponds to the beginning of the second caffeine test.

[d] Statistically significant change compared with the corresponding values of the first caffeine test.

test (Table 1). According to the protocol supported by the European MH Group, these 22 patients were classified as MHS.

Twenty-two other muscle bundles from the same MHS patients were tested with the second halothane test and had similar contracture threshold (0.61 ± 0.14 g at 2% halothane) as the first halothane test despite an interval of 30 min between the two tests. Fourteen muscle bundles tested with the second caffeine test responded positively (Table 1, top). In contrast, eight of the 22 muscle bundles tested with the second caffeine test did not develop any contracture at 2 mM caffeine, leading to false-negative results. The caffeine contracture threshold was shifted to a higher concentration of 3 mM caffeine for six muscle bundles and 4 mM caffeine for two muscle bundles. Therefore, two subgroups were defined from these 22 MHS patients as patients with two successive positive caffeine tests (group 1, $n = 14$) (Table 1, top) and patients with the former caffeine test positive and the latter negative (group 2, $n = 8$) (Table 1, bottom). Thirty-four patients did not develop any significant contracture at the above concentrations and were classified as MHN (Table 2).

Resting Membrane Potentials

In MHS patients, resting membrane potentials from all fiber segments of group 1 ranged between −66 and −87 mV at 30 min after biopsy (Table 1, top) (Figure 1). At 75 min after biopsy, fiber segments from 11 of 14 MHS patients repolarized to values between −69 and −88 mV. Values of resting membrane potentials at the two different times after bi-

Table 2. Time-Dependent Changes in Muscle Bundles From 34 Malignant Hyperthermia–Nonsusceptible Patients

	30 Min after biopsy				75 Min after biopsy			
Patient No.	Caffeine threshold (mM)	Resting potential (mV)	Twitch tension (g)	32 mM caffeine (g/cm²)	Caffeine threshold (mM)	Resting potential (mV)	Twitch tension (g)	32 mM caffeine (g/cm²)
1	4	−63.7 ± 2.8 (14)	1.00	31	8	−68.5 ± 5.2 (14)	0.90	50
2	8	−71.0 ± 6.7 (13)	1.00	36	4	−75.0 ± 6.2 (11)	0.80	64
3	8	−73.7 ± 7.5 (14)	1.20	77	8	−74.1 ± 7.3 (13)	1.00	120
4	4	−74.6 ± 7.9 (15)	1.00	38	4	−73.4 ± 8.1 (17)	1.00	37
5	3	−72.6 ± 7.5 (15)	1.10	41	4	−70.0 ± 7.4 (15)	1.00	40
6	8	−70.6 ± 4.9 (15)	0.95	28	4	−73.0 ± 6.0 (15)	0.80	64
7	8	−80.4 ± 6.8 (15)	3.00	42	8	−76.8 ± 4.3 (15)	2.00	71
8	8	−80.4 ± 5.8 (15)	2.30	46	4	−80.2 ± 5.4 (15)	2.30	37
9	3	−71.8 ± 3.9 (15)	1.10	51	3	−72.9 ± 7.6 (15)	1.00	56
10	4	−77.6 ± 7.1 (15)	1.40	66	4	−85.8 ± 8.0 (15)	1.30	40
11	4	−76.4 ± 6.3 (15)	1.00	55	4	−80.2 ± 5.8 (15)	1.40	54
12	4	−78.8 ± 5.0 (15)	1.60	38	4	−83.0 ± 5.2 (15)	1.60	36
13	4	−74.1 ± 3.9 (12)	1.60	87	4	−68.6 ± 3.9 (12)	1.70	85
14	3	−71.3 ± 6.5 (12)	1.90	80	3	−77.0 ± 3.7 (12)	2.50	116
15	8	−77.6 ± 5.0 (15)	1.00	41	8	−72.8 ± 3.0 (15)	1.60	95
16	4	−75.6 ± 4.4 (15)	1.00	37	8	−76.5 ± 5.4 (12)	1.00	50
17	4	−77.1 ± 5.1 (15)	1.20	42	4	−80.4 ± 3.0 (13)	1.20	40
18	4	−75.8 ± 3.6 (12)	1.50	87	8	−81.2 ± 6.3 (14)	1.70	88
19	16	−71.6 ± 4.4 (12)	1.20	65	16	−70.4 ± 2.1 (12)	1.80	42
20	8	−75.7 ± 4.0 (15)	1.00	33	8	−82.8 ± 4.0 (15)	1.60	31
21	8	−77.2 ± 5.5 (15)	1.60	67	8	−75.1 ± 4.1 (15)	4.00	75
22	8	−75.0 ± 2.7 (14)	2.10	100	8	−77.8 ± 4.5 (14)	1.10	112
23	3	−77.6 ± 4.8 (15)	2.40	41	3	−80.3 ± 6.3 (15)	2.00	69
24	8	−72.9 ± 4.3 (12)	1.00	74	8	−75.2 ± 4.3 (16)	0.80	81
25	4	−81.6 ± 4.4 (15)	2.10	157	8	−81.5 ± 3.9 (15)	1.90	111
26	4	−82.2 ± 3.8 (18)	5.00	75	4	−88.5 ± 4.8 (15)	4.50	68
27	4	−80.1 ± 3.9 (19)	1.50	80	4	−80.2 ± 2.6 (17)	2.50	90
28	4	−79.3 ± 3.4 (16)	2.50	140	3	−79.7 ± 3.8 (15)	2.20	127
29	8	−89.3 ± 7.1 (12)	3.00	58	8	−85.4 ± 6.7 (11)	5.50	60
30	4	−87.2 ± 5.7 (15)	3.10	135	4	−82.5 ± 3.2 (15)	3.20	110
31	4	−84.8 ± 3.6 (13)	6.00	150	4	−81.8 ± 3.3 (15)	4.00	112
32	4	−86.0 ± 5.1 (16)	2.00	50	4	−82.4 ± 3.3 (15)	3.00	60
33	8	−85.1 ± 3.6 (15)	2.50	64	8	−84.7 ± 4.1 (15)	4.70	60
34	8	−87.5 ± 4.4 (15)	2.10	160	8	−87.6 ± 4.7 (15)	2.30	93
Mean	5.7	−77.5	1.88	69.7	5.8	−78.3	2.05	71.8
± SD	2.7	5.6	1.13	38.0	2.7	5.3	1.3	28.4

Values for resting potential represent mean ± SD for each patient. Numbers of values are given in parentheses.
Caffeine threshold expressed in millimolar is the caffeine concentration that induced muscle contracture ≥0.2 g.
[a] Thirty minutes after biopsy corresponds to the beginning of the first caffeine test.
[b] Seventy-five minutes after biopsy corresponds to the beginning of the second caffeine test.

opsy remained unchanged for patients 3, 4, and 10. In group 2 (Table 1, bottom) (Figure 1), resting membrane potentials recorded before the first caffeine test did not significantly differ from those of group 1. In contrast, all fiber segments significantly depolarized at 75 min after biopsy, and the average potential of −65 mV was significantly different from group 1 values. In addition, fiber segments of muscle bundles from patients 1 and 2 of group 2 were depolarized to values below −60 mV. Thus supramaximal electrical stimulation resulted in little contractile force. Differences in resting potentials at 30 and 75 min after biopsy were calculated for each group of MHS patients. It was found that a decrease in resting potentials of 5 mV between the two tests in an estimated population of MHS patients may predict false-negative results for the second caffeine test. Sensitivity and specificity for this given value were 75% and 97.5%, respectively.

In MHN muscle bundles, resting membrane potentials recorded before the two successive caffeine tests were not significantly different (Table 2). These values were similar to those of group 1 as well as to the first caffeine test of group 2 in the MHS patients.

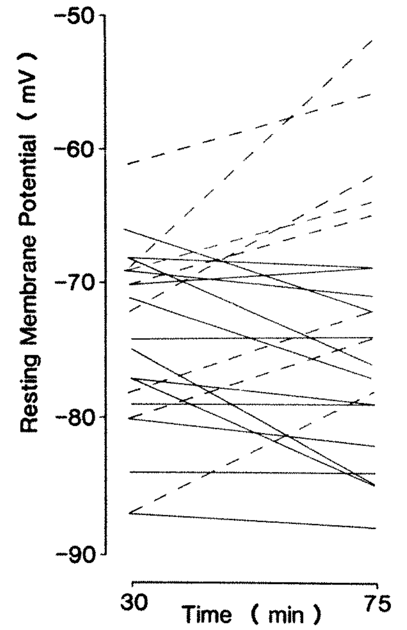

Figure 1. Values for resting membrane potential are connected in each malignant hyperthermia–susceptible patient at 30 and 75 min after biopsy. *Solid lines* refer to connected membrane potentials in each patient of group 1 (*n* = 14). *Dashed lines* refer to connected membrane potentials in each patient of group 2 (*n* = 8). Time-induced depolarization of muscle bundles of at least 5 mV can predict false-negative results of the second caffeine test.

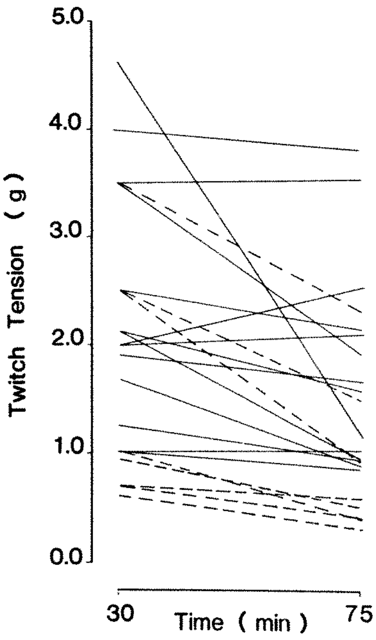

Figure 2. Values for twitch tension are connected in each malignant hyperthermia–susceptible patient at 30 and 75 min after biopsy. *Solid lines* refer to connected values in each patient of group 1 (*n* = 14). *Dashed lines* refer to connected values in each patient of group 2 (*n* = 8). The decrease in twitch tension with time after biopsy does not predict false-negative results of the second caffeine test. All specimens with less than 1 g twitch tension at the first caffeine test depolarized with time and gave false-negative results at the second caffeine test.

Force Displacement Measurements

In the MHS patients, group 1 had high (≥1 g) predrug twitch tension amplitude, and this amplitude was not significantly reduced with time after biopsy (Figure 2). In contrast, the amplitude of twitch tension in group 2 was initially less than in group 1, and this amplitude was further decreased at 75 min after biopsy ($P < 0.05$) (Figure 2). In group 1, increasing the voltage to supramaximal response did not significantly change for the caffeine tests performed at the two different times after biopsy. The mean values were 29 ± 12 V for caffeine tests performed earlier and 39 ± 14 V for the second caffeine tests. In group 2, the amplitude of the voltage was similar to that observed in group 1 in the first series of caffeine tests (32 ± 16 V). In contrast, the tests performed later required higher voltage (50 ± 18 V). In both groups no significant difference was observed between the maximum contracture induced by 32 mM caffeine in the two tests.

Correlation coefficients for resting membrane potentials versus twitch tension at the two different times after biopsy are given in Table 3. No correlation was found for group 1, whereas there was a positive correlation in group 2 for twitch tension at 30 and 75 min after biopsy.

Muscle bundles from the 34 MHN patients had high (≥1 g) predrug twitch tension amplitude, and this amplitude was not significantly reduced at 75 min after biopsy. In this group, the amplitude of the voltage was similar in the two caffeine tests (33.3 ± 14 V vs 45.1 ± 17 V). Furthermore, the maximum contracture induced by 32 mM caffeine was not different in the two tests (Table 2).

Discussion

The main finding of the current study is that a time-related depolarization of MHS muscle fibers influences the concentration of caffeine required to induce a contracture. Time-induced depolarized MHS fibers became less sensitive to caffeine, and this measurable factor might provide a useful additional variable for identification of the physiologic state of transected fibers used for in vitro pharmacologic tests. The results obtained both in the MHN group and in group 1 of MHS muscle bundles are in agreement with those of Lehmann-Horn and Iaizzo who found that fiber segments of muscle bundles repolarized with time after dissection (7). These authors state that fiber segments less than 2.5 cm long were not considered optimal for use in physiologic

Table 3. Correlation Coefficients for Resting Membrane and Twitch Tension of Muscle From the 22 Malignant Hyperthermia Susceptible Patients

Group of patients	Covariate	No. of muscle bundles	Twitch tension 30 min after biopsy	No. of muscle bundles	Twitch tension 75 min after biopsy
1	Resting potential	14	0.33	14	0.48
2	Resting potential	8	0.92[a]	8	0.83[a]

[a] $P < 0.01$.

investigations as the segment length was directly related to the level at which the fibers repolarized. In our study, even the fibers in group 1 were depolarized (−70 mV compared with −85 to −90 mV in intact fibers). Perhaps fiber segments less than 2.0 cm long may be too short for use in the in vitro contracture test. However, a previous report by these authors demonstrated that (a) time-induced variation of resting membrane potential was not correlated with the in vitro caffeine test, and (b) not all long fiber segments (≥2.5 cm) from MHS patients repolarized to normal values (7).

In animal species, depolarization consecutive to transection of skeletal muscle has been well documented, but the results differ from our findings (8–11). A study on MHS pigs reported that results of the in vitro contracture test are independent of the resting membrane potential (10). Other studies observed that intact bundles from MHS limb muscles exhibited an apparent decreased sensitivity to caffeine when compared with responses of cut preparations (11,12). However, these studies differed from the current study in many ways, including the type of muscle used and the manner in which the protocol was performed.

The need to continuously monitor the quality of MHS muscle preparations has already been reported, and studies concluded that MHS muscle is particularly injury-sensitive and deteriorates more rapidly with time than normal muscle (8,12,13). The current study may indicate that MHS muscle bundles deteriorate at even shorter periods after biopsy. At 30 min after biopsy, all MHS cut muscle bundles produced twitch tension and maximum tension equal to that of normal cut bundles, but some of them deteriorated 75 min later. This emphasizes the importance of carefully monitoring any measurable factor postulated as being a possible indicator of the good quality of muscle bundles. Hence, resting membrane potential could be a useful variable to monitor to improve reliability of muscle testing.

A direct relationship between the depolarization of the fibers and the shift in contracture response of the muscle to caffeine is not a logical conclusion as it is well known that in healthy muscle fiber, potassium-induced depolarization of muscle increases its sensitivity to caffeine (14,15). In fact, the loss in contracture response to caffeine is probably not due to depolarization but to some other factors that lead to muscle deterioration within a short period of time. The fibers (a) became depolarized, (b) produced less force when stimulated, and (c) had reduced sensitivity to caffeine, which itself is thought to have a direct effect on the sarcoplasmic reticulum (14). These results further support arguments to exclude muscle bundles with less than 1 g twitch tension for diagnostic test. Additional studies are required to verify the role of an initial fiber depolarization on the results of the in vitro contracture test and to examine the influence of muscle length on both resting membrane potential and sensitivity to caffeine in human muscle. On the other hand, it appears from other studies that the halothane test is the most reliable diagnostic test for MH susceptibility as more patients have an abnormal response to halothane than to caffeine (16,17). One possible explanation for this discrepancy could be a higher decreased sensitivity of injured muscle to caffeine than to halothane.

In conclusion, we found that if cut fiber specimens depolarize with time after biopsy, these preparations become less sensitive to caffeine, leading to caution in the interpretation of the in vitro caffeine contracture test.

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References

1. European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. Br J Anaesth 1984;56:1267–9.
2. Melton AT, Martucci RW, Kien ND, Gronert GA. Malignant hyperthermia in humans. Standardization of contracture testing protocol. Anesth Analg 1989;69:437–43.
3. Fletcher JE, Rosenberg H, Hilf M. Effects of midazolam on directly stimulated muscle biopsies from control and malignant hyperthermia positive patients. Can Anaesth Soc J 1984;31:377–81.
4. Ording H, Hansen U, Skövgaard LT. Age, fiber type composition and in vitro contracture responses in human malignant hyperthermia. Acta Anaesthesiol Scand 1988;32:121–4.

5. Ording H. Influence of propanolol on the in vitro response to caffeine and halothane in malignant hyperthermia-susceptible muscle. Acta Anaesthesiol Scand 1989;33:405–8.
6. Adnet P, Krivosic-Horber R, Haudecoeur G, Reyford H, Adamantidis M, Dupuis B. Diltiazem and nifedipine reduce the in vitro contracture response to halothane in malignant hyperthermia susceptible muscle. Can J Anaesth 1990;137:556–9.
7. Lehmann-Horn F, Iaizzo PA. Resealed fiber segments for the study of the pathophysiology of human skeletal muscle. Muscle Nerve 1990;13:222–31.
8. Gallant EM, Fletcher TF, Goettl VM, Rempel WE. Porcine malignant hyperthermia: cell injury enhances halothane sensitivity of biopsies. Muscle Nerve 1986;9:174–84.
9. Hubbard JI, Wilson DF. Neuromuscular transmission in a mammalian preparation in the absence of blocking drugs and the effect of *d*-tubocurarine. J Physiol (Lond) 1973;228:307–25.
10. Iaizzo PA, Lehmann-Horn F. The in vitro determination of susceptibility to malignant hyperthermia. Muscle Nerve 1989; 12:184–90.
11. Nelson TE, Bedell DM, Jones EW. Porcine malignant hyperthermia: effects of temperature and extracellular calcium concentration on halothane-induced contracture of susceptible skeletal muscle. Anesthesiology 1975;42:301–6.
12. Britt BA, Scott E, Frodis W, Clements MJ, Endrenyi L. Dantrolene-in vitro studies in malignant hyperthermia susceptible and normal skeletal muscle. Can Anaesth Soc J 1984;31:130–54.
13. Iaizzo PA, Klein W, Lehmann-Horn F. Fura-2 detected calcium and its correlation with contracture force in skeletal muscle from normal and malignant hyperthermia susceptible pigs. Pflügers Arch 1988;411:648–53.
14. Lüttgau HC, Oetliker H. The action of caffeine on the activation of the contractile mechanism in striated muscle fibers. J Physiol (Lond) 1968;194:51–74.
15. Nelson TE, Denbororough MA. Studies on normal human skeletal muscle in relation to the pathopharmacology of malignant hyperpyrexia. Clin Exp Pharmacol Physiol 1987;4:315–22.
16. Rosenberg H, Reed S. In vitro contracture tests for susceptibility to malignant hyperthermia. Anesth Analg 1983;62:415–20.
17. Ording H, Ranklev E, Fletcher R. Investigation of malignant hyperthermia in Denmark and Sweden. Br J Anaesth 1984;56: 1183–9.

Lecture Practices in United States Anesthesiology Residencies

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We obtained data on lecture practices from 100 of the 110 university-affiliated anesthesiology residency programs certified in the United States in 1988. Of these residency programs, 36% had a majority of their lectures before the operating room schedule began, 57% had no lectures at all in this early time slot, and 78% had morning lectures at least once a week in conjunction with a delayed operating room start. Seventy-one percent of programs had one or more afternoon lectures each week. An attendance of more than 80% was reported in 66% of the programs for morning lectures and in 50% of the programs for afternoon lectures, which is a significant difference. Aggregate pass rates on the American Board of Anesthesiology written examinations in 1987 and 1988 correlated significantly with morning-lecture attendance, but not with afternoon-lecture attendance, number of lecture days per week, or mandatory lecture attendance. These findings suggest the need for further study and definition of the role of lectures in resident education in anesthesiology.

(Anesth Analg 1992;74:112–5)

Lectures are an important means for conveying and reinforcing knowledge in graduate and undergraduate medical education (1). The scheduling of lectures for residents in anesthesiology encounters impediments unique to the specialty. Resident participation in surgical cases takes precedence over other program activities. Also because the number, spacing, and duration of operations are very variable and outside the anesthesiology department's control to a large extent, lectures cannot realistically be scheduled during hours when operating rooms (ORs) are likely to be busy. Lectures held before the hospital's designated OR start time are hampered by the early starting time required to finish the lecture and yet allow time for preparing patients and ORs for the morning cases. In the afternoons, however, different ORs may finish at different times; no matter what the hour, some residents may still be busy, whereas others may have finished work hours before. As a guide to balancing the educational needs of our residents with our service obligations to the surgeons and the hospital, we surveyed all university-affiliated anesthesiology residency programs in the United States to ascertain the range of their lecture practices.

Methods

Questionnaires were sent to all listed members of the Society of Academic Anesthesia Chairmen in late 1988. This survey included 110 anesthesiology residencies based at medical schools in the United States and Puerto Rico. Responses of each chairman or program director to 30 questions concerning current resident lecture practices and performance on the 1987 and 1988 written examinations of the American Board of Anesthesiology were tabulated and analyzed using Abstat software on an IBM PS/2 model 50 computer with 20-megabyte hard disk. Single and multiple linear regression, χ^2, and Mann-Whitney analyses were used for statistical evaluation of results (2).

Results

Responses were received from 100 of the 110 active programs that were surveyed (a 91% participation rate). Twenty-four of the 30 questions asked in the survey are listed in Table 1; each question is accompanied by a frequency distribution of the responses provided. The frequencies shown in Table 1 and summarized in the text that follows are provided both as absolute values and as a percentage of the total number of responses to that question. As some

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A partial presentation of these findings was made at the annual meeting of the American Society of Anesthesiologists, October 1989, in New Orleans, Louisiana.

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Table 1. Survey Questions and Responses

1. How many days per week do you have lectures for residents?		
One:	16	(16%)
Two:	31	(32%)
Three:	27	(27%)
Four:	15	(15%)
Five:	10	(10%)
Total:	99	(100%)
2. What is the usual start time for surgery?		
7:00 AM:	7	(7%)
7:15 AM:	2	(2%)
7:30 AM:	50	(50%)
7:45 AM:	13	(13%)
8:00 AM:	28	(28%)
Total:	100	(100%)
3. Do you have early AM lectures (i.e., before the usual OR start time)?		
Yes:	43	(43%)
No:	57	(57%)
Total:	100	(100%)
4. Are the majority of your lectures given as early AM lectures?		
Yes:	35	(36%)
No:	63	(64%)
Total:	98	(100%)
5. What is the start time of your early AM lectures?		
6:00 AM:	3	(7%)
6:15 AM:	3	(7%)
6:30 AM:	9	(21%)
6:45 AM:	13	(30%)
7:00 AM:	15	(35%)
Total:	43	(100%)
6. What is the length of your early AM lectures?		
15 min:	3	(7%)
30 min:	18	(42%)
45 min:	13	(30%)
60 min:	9	(21%)
Total:	43	(100%)
7. Do you have late AM lectures (before a delayed OR start)?		
Twice a week:	3	(3%)
Once a week:	75	(75%)
Every 2 weeks:	3	(3%)
None:	19	(19%)
Total:	100	(100%)
8. What is the length of your late AM lectures?		
30 min:	1	(1%)
45 min:	6	(8%)
60 min:	53	(67%)
75 min:	4	(5%)
90 min:	7	(9%)
120 min:	5	(6%)
240 min:	3	(4%)
Total:	79	(100%)
9. What percentage of residents attend AM lectures?		
0–50:	4	(5%)
51–70:	9	(11%)
71–80:	15	(18%)
81–90:	20	(24%)
91–100:	36	(42%)
Total:	84	(100%)
10. Do you have afternoon lectures?		
Yes:	71	(71%)
No:	29	(29%)
Total:	100	(100%)
11. How many days per week do you have afternoon lectures?		
One:	33	(47%)
Two:	28	(39%)
Three:	8	(11%)
Four:	2	(3%)
Total:	71	(100%)
12. What is the start time of your afternoon lectures?		
Noon–2:00 PM:	3	(4%)
2:01 PM–3:00 PM:	10	(15%)
3:01 PM–4:00 PM:	40	(58%)
4:01 PM–5:00 PM:	13	(19%)
5:01 PM–6:00 PM:	3	(4%)
Total:	69	(100%)
13. What is the length of your afternoon lectures?		
60 min:	41	(58%)
61–90 min:	12	(17%)
91–120 min:	15	(21%)
121–180 min:	3	(4%)
Total:	71	(100%)
14. What percentage of residents attend afternoon lectures?		
0–50:	7	(10%)
51–70:	9	(13%)
71–80:	19	(27%)
81–90:	13	(18%)
91–100:	23	(32%)
Total:	71	(100%)
15. Who provides coverage for residents to attend afternoon lectures?		
CRNAs only:	10	(14%)
Residents only:	1	(1%)
Faculty only:	7	(10%)
CRNAs + residents:	6	(9%)
CRNAs + faculty:	31	(44%)
Residents + faculty:	4	(6%)
CRNAs + residents + faculty:	11	(16%)
Total:	70	(100%)
16. Is lecture attendance mandatory?		
Yes:	74	(76%)
No:	23	(24%)
Total:	97	(100%)
17. What percentage of lectures are given by residents?		
0:	11	(12%)
1–10:	28	(30%)
11–25:	24	(26%)
26–50:	23	(25%)
51–100:	6	(7%)
Total:	92	(100%)
18. How many lectures were given by visiting professors last year?		
1–5:	27	(27%)
6–10:	36	(37%)
11–20:	27	(27%)
21–30:	3	(3%)
31–40:	6	(6%)
Total:	99	(100%)
19. How many lectures did each of your faculty give last year?		
1–2:	23	(25%)
3–4:	34	(37%)
5–6:	16	(17%)
7–8:	8	(9%)
9–12:	7	(8%)
13–20:	4	(4%)
Total:	99	(100%)
20. Do you have lectures on Saturday?		
Yes:	9	(9%)
No:	90	(91%)
21. Do you have lectures after 6 PM?		
Yes:	28	(29%)
No:	69	(71%)
Total:	97	(100%)
22. How often does journal club meet?		
Weekly:	3	(3%)
Monthly:	78	(79%)
Bimonthly:	5	(5%)
Quarterly:	3	(3%)
None:	10	(10%)
Total:	99	(100%)
23. What percentage of your residents passed the written examination in 1987?		
0–50:	2	(2%)
51–70:	4	(5%)
71–80:	12	(15%)
81–90:	14	(17%)
91–100:	51	(61%)
Total:	83	(100%)
24. What percentage of your residents passed the written examination in 1988?		
0–50:	4	(5%)
51–70:	3	(4%)
71–80:	14	(17%)
81–90:	10	(13%)
91–100:	48	(61%)
Total:	79	(100%)

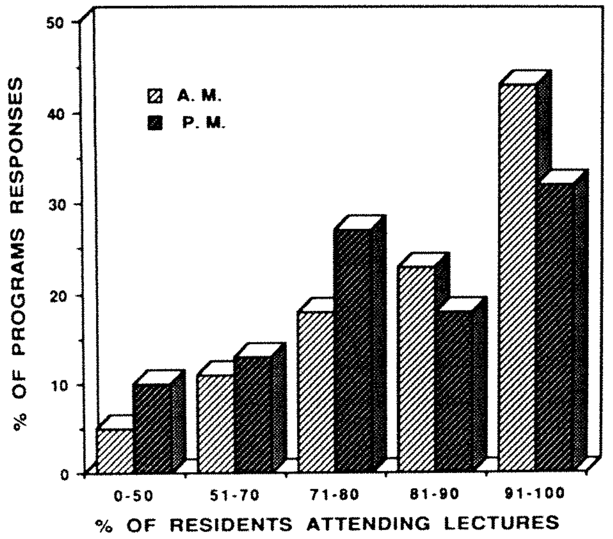

Figure 1. Frequency distribution of responses to questions concerning the percentage of residents attending morning or afternoon lectures.

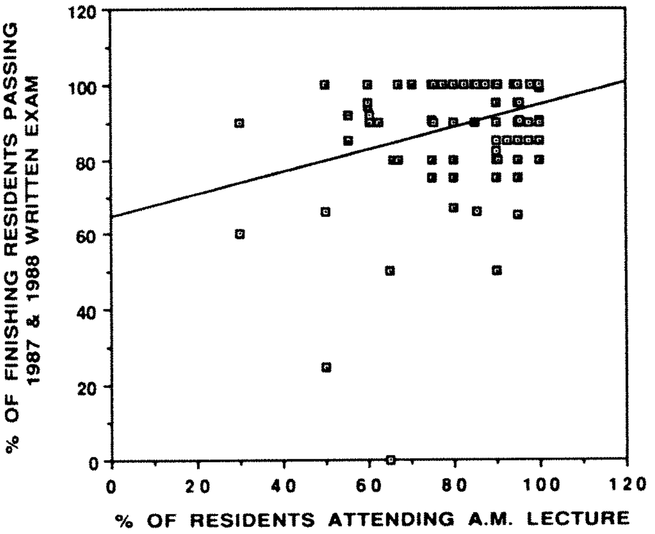

Figure 2. Percentage of residents passing the 1987 or 1988 written examinations plotted as a function of attendance at morning lectures. The values obtained from this single linear regression are $y = 0.30x + 64$, $r = 0.30$, $P < 0.0003$.

questions were not applicable to certain programs, or as data were not provided for other reasons, the number of responses to a given question was often less than 100.

All 100 programs had lectures at least 1 day per week. Despite the early hour, 36% of programs scheduled more than half of their weekly lectures before the usual OR starting time (early-morning lecture). Although the majority of such lectures started at 6:45 or 7:00 AM, 14% of the programs began their early-morning lectures at 6:15 AM or earlier. The length of early-morning lectures ranged from 15 to 60 min, with more than half lasting 30 min. On the other hand, 57% of programs had no early-morning lectures scheduled. However, in 78% of programs surveyed, the OR starting time was delayed by at least 1 h on one or more days per week specifically to facilitate lectures (i.e., late-morning lectures). These late-morning lectures were significantly longer than the early-morning ones ($P < 0.02$, Mann-Whitney), lasting between 30 min and 240 min (median, 60 min).

Seventy-one percent of programs surveyed had one or more afternoon lectures each week. The start time for afternoon lectures ranged from 2 to 6 PM, with a majority of lectures starting at 4 PM or later. The minimum duration reported (60 min) was also the most frequent length of the lecture.

The attendance estimates differed for morning and afternoon lectures (Figure 1). It was reported that more than 80% of residents attended the morning lecture in 66% of the programs. However, resident attendance at afternoon lectures was reported to be better than 80% in only 50% of the programs, despite the fact that most programs provided coverage by attending staff or CRNAs or both. This difference in attendance between morning and afternoon lectures was statistically significant ($P < 0.05$ by χ^2-analysis).

As shown in Figure 2, the tendency of programs with higher estimated attendance at morning lectures to have higher pass rates in 1987 and 1988 was highly significant statistically ($P < 0.003$ by multiple linear regression), although the strength of the correlation was low ($r = 0.30$). On the other hand, there was negligible association between pass rates and afternoon lecture attendance (Figure 3). We also found no significant correlation of pass rates with various other measures of lecture practice—number of lecture days per week, number of afternoon lectures per week, presence/absence of early- or late-morning or late-afternoon lectures or of mandatory attendance at lectures.

Discussion

Organizing and implementing lectures for an anesthesiology residency program pose difficult problems. The wide range of practices shown by our fairly complete sampling of university-based American programs suggests that there are no generally agreed-upon solutions. Although all programs for which responses were received do have lectures, there were considerable variations in the number and scheduling. There was limited reliance on early-morning lectures, i.e., those held before the usual OR start. This finding is surprising, because this time slot is available every working day and minimizes compet-

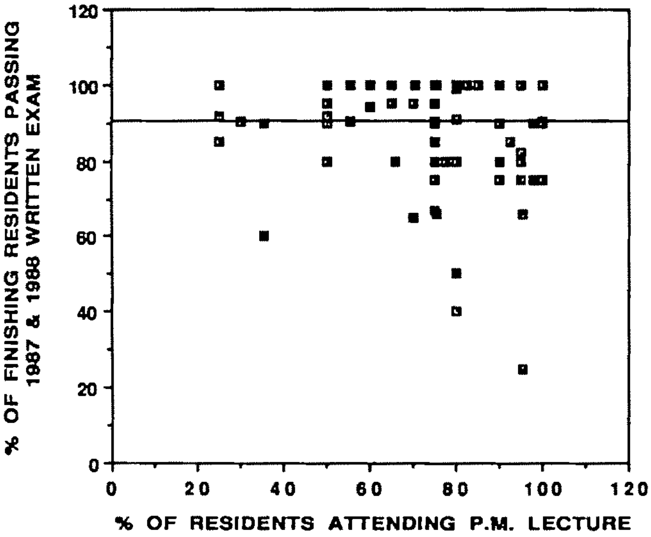

Figure 3. Percentage of residents passing the 1987 or 1988 written examinations plotted as a function of attendance at afternoon lectures. The values obtained from this single linear regression are $y = 0.005x + 90$, $r = 0.01$, $P < 0.95$.

ing clinical obligations that erode attendance. On the other hand, the more widely used late-morning format also offers protected time at a more reasonable hour. The increased length of late lectures may compensate for their decreased frequency, especially in programs that have fewer overall lecture sessions.

The differences in attendance at morning and afternoon lectures are probably accounted for largely by the latter's lack of protection from conflicting demands on residents' time. The observed association between a program's morning- (but not afternoon-) lecture attendance and the examination performance of its residents—to the extent that the finding is valid (see discussion below)—suggests that such morning lectures produce a significant beneficial effect on residents' knowledge. Positive associations between morning-lecture attendance and test scores have been demonstrated for undergraduate medical education (3–5). That a benefit could not be demonstrated for afternoon lectures may reflect effects either of the time of day per se (such as the influence of fatigue), or of secondary factors (e.g., the smaller number of afternoon lectures may have diluted their influence on educational outcome; or attendance at morning lectures reflected residents' assignment to the university hospital and thus time spent in the environment most conducive to learning).

Our findings concerning the value of lecture practices in relation to examination performance must be considered as only tentative. Survey responses were no doubt imprecise and even inaccurate to the extent that record keeping and retrieval (and/or recall) were inconsistent from one program to another. Also, the low values of correlation coefficient indicate that test scores are substantially influenced by variables other than lecture attendance. (Because $r^2 = 0.09$, 91% of the agreement between observed and predicted values of examination scores still remains to be accounted for by other factors that contribute to outcome.) Lecture quality, resident aptitude, and teaching/learning modalities other than lectures are among the likely candidates for the principal outcome-related variables not assessed in our survey. Clearly, a study design that controls for such confounding variables will be required to evaluate more definitively the contribution of lectures to resident education and to academic performance in anesthesiology.

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References

1. Brent DA. The residency as a developmental process. J Med Educ 1981;56:417–22.
2. Bourke GJ, Daly LE, McGilvray J. Interpretation and uses of medical statistics. 3rd ed. London: Blackwell, 1985:302.
3. Sade RM, Stroud MR. Medical student attendance at lectures: effect on medical school performance. J Med Educ 1982;57:191–2.
4. Newman SN, Schuman NJ, Fields WT, Nunez L. Dental students' grades and their relationship to classroom attendance. J Dent Educ 1981;45:360–1.
5. Glanz K, Fiel SB. Effect of attendance at lectures on medical student performance. J Med Educ 1984;59:516–8.

Anesthesiology Journals, 1992

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The intellectual and professional stature of any branch of human endeavor can be judged by the quality of the written word that it produces. Within the liberal arts, the written word as it appears in monographs and books may be an especially useful guide in various fields of special interest. Not so in biomedical areas. In biomedical areas, the written word as it appears in journals more accurately reflects the health, the vigor, and even the scientific validity of a special discipline than does the written word as it appears in monographs and textbooks. This is the case because what appears in peer-reviewed biomedical journals (quality of the written word in journals can be assured only by peer review) represents the cutting edge in that specialty. The written word in these journals casts light on what those who are engaged in peer review regard as new, important, and valid in that field. What is published in the journals of a medical specialty defines for better or for worse the standard of contemporary excellence within the discipline. This is as true in anesthesiology as in any other medical discipline. Pausing to reflect on the state of the art of anesthesiology as evidenced by the quality of the written word in its journal thus provides a useful and indeed necessary opportunity for asking ourselves: where do we stand? Where are we going?

Measuring something as subjective as quality of the written word is as fraught with dangers as attempting to measure beauty. Perhaps one qualification might be 40 years in the specialty, much of it as an earnest student and observer of medical journals to see what makes them tick and what makes them good, great, or not so good or great. Not just anesthesiology journals either, but all types of medical journals. It also might be helpful in judging the quality of anesthesiology journals to have spent 26 years both as editor and editor-in-chief of *Anesthesiology* and as editor-in-chief of *Anesthesia and Analgesia*, an experience guaranteed to hone one's sensibilities with regard to quality of the written word.

What, however, criteria can be used for determining something as potentially nebulous as quality of the written word in anesthesiology journals? The appropriate criteria are best based by defining, first, the function of anesthesiology journals. Having defined function, one can then determine how well anesthesiology journals are, or are not, fulfilling their function.

The main function of a first class medical specialty journal is simply to educate its readers. It does so by publishing information that is original, important, and valid. Each of these three attributes is a sine qua non. The wheel does not need to be reinvented every decade. Inconsequential, specious, or irrelevant data do not deserve public attention. And, of course, the data presented and the conclusions drawn from them must be impeccable. Fulfillment of these three criteria can be seen in published materials reporting in vitro data as well as in vivo experiments involving animal life ranging from unicellular organisms to humans, the latter as volunteers or as patients. The criteria of originality, significance, and validity can be met equally well in papers reporting epidemiologic, demographic, or historical information, as well as in papers that present new analytic techniques, new patient care delivery systems, or brief case reports.

How well are today's anesthesiology journals succeeding in 1992 in carrying out the primary function of any truly first-class medical journal: education of the reader by publication of new, important, and valid information? If one looks carefully, meticulously and, above all, objectively at today's anesthesiology journals as well as those published in bygone years, one discerns a number of changes that have taken place in the past and still are taking place, some not necessarily for the better.

One of the changes taking place in English-language anesthesiology journals throughout most of the world involves the quality of presentation, the quality of the text itself, of materials being published. This involves, amongst other things, clarity, accuracy, and logic, to say nothing of felicity of style. Dispassionate scrutiny of our journals today leads

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one to the depressing but unavoidable conclusion that there has been and is a continuing erosion in use of the English language. This deterioration is perhaps especially evident in the proliferation of specialty jargon. Today, patients, not drugs, are increasingly being administered. Patients, not anesthesia, are being induced with thiopental. With succinylcholine, too. Patients are put on ventilators. Patients are aspirated. So are catheters. Combine these misuses of words with a style of presentation that resembles a barrel of bolts rolling downhill and we have texts no longer pleasing to the eye or a pleasure to read and often inscrutable in meaning.

Other changes are also taking place. One is substantially more important. A subtle change, yes, but one that commands, indeed, demands attention. It can be discerned only if one looks closely at not just one or two anesthesiology journals but rather at the totality of English-language journals. This change involves *all* English-language anesthesiology journals, some more than others, but all are involved. Furthermore, this important change cannot be readily recognized for what it is unless one is intimately acquainted with what has been published in the past in our specialty. Only by considering the level of success in the past in meeting the function of anesthesiology journals as defined can one judge how successful we are today in fulfilling the challenges involved in publication of anesthesiology journals. And only then, too, can one estimate where we will likely be tomorrow in terms of how well anesthesiology journals fill their role and carry out their function.

Knowledge of what has preceded in the past in our journals, when combined with knowledge of what is being published today throughout the entirety of anesthesiology literature, is essential if one is to judge the ability of our journals to consistently publish materials not only valid but, equally important, original. The three criteria of publishability represent the three-legged stool of excellence. A one-legged stool is not a stool. Excellence cannot be judged on the basis of only some of its constituent parts. To judge today's standards of excellence in the anesthesiology literature requires a perspective based on the long-term view that includes intimate knowledge of what has preceded. If one looks at a forest for only 2 or 3 years, little will be seen to change. Look at a forest for 20–25 years and one can see what is really happening.

Acquaintance with the paleoanesthesiology literature is, then, essential as a basis for the development of real understanding and perspective of what has happened and is happening in anesthesiology journals. When, for example, one examines closely and objectively anesthesiology journals in the 1950s and 1960s, one finds they were remarkably successful in the consistency with which they published materials that were—*for their times*—original, important, and valid. True, when one looks with the aid of a 1992 retrospectoscope at articles that were published in the 1950s and 1960s, they seem naive, amateurish, and superficial. Yes, but standards of excellence change with time as research methods develop and as the questions being addressed become more complex and sophisticated. Before judging too harshly the anesthesiology literature of 30 years ago—in the 1960s—consider how anesthesiologists 30 years from now—in the 2020s—will view what we publish today in the 1990s. Be humble.

Dispassionate scrutiny of anesthesiology journals today and those of 30 or so years ago leaves one with the strong clinical impression that something very fundamental has changed. The validity of what we publish, both methodologic and statistical validity, is not one of the things that have changed appreciably over the years if one takes into account contemporaneous standards of excellence. What one does see, however, are internationally, specialty-wide decreases in both originality and significance of articles that are being published. The number of excellent articles being published has increased as the specialty has grown. What has decreased—and markedly decreased—is the percentage of articles being published that provide the reader with information identifiably new, important, and valid. In the decades between 1950 and 1970, the percentage of materials published in anesthesiology journals that were lacking—*by contemporaneous standards*—in originality and importance, was less than it is today. Today, not in any one journal but specialty-wide, the incidence of originality has decreased and the incidence of triviality has increased. This is appalling, but the reality of this change is indisputable, though unquantifiable, if one but looks at the articles being published in today's anesthesiology journals in the context of criteria of excellence as defined and as seen in the past.

A great deal of what is being published internationally today in our specialty journals is conspicuous for being quite forgettable, quite nonmemorable—materials that do not really warrant publication. This can be seen in all English-language journals, some more so than others, but every current journal is affected. We are today publishing more materials that we can do without than we have in the past.

Scrutiny of the vacuous if not fatuous space-occupying lesions that clutter the pages of our journals reveals that they appear in four forms:

1. Articles that consist of rediscovery of the wheel in various forms or disguises. These are the papers that are not really original, if one is as acquainted

Table 1. Growth of Anesthesia Literature by Decades[a]

	1922	1932	1942	1952	1962	1972	1982	1992
Anesth Analg (1922)	6	6	6	6	6	6	12	12
Br J Anaesth (1923)		4	4	4	12	12	12	12
Anesthesiology (1940)			6	6	6	12	12	12
Anaesthesia (1946)				4	4	4	12	12
Can J Anaesth (1954)					4	4	6	8
Acta Anaesthesiol Scand (1957)					4	4	6	8
Anaesth Intensive Care (1973)							4	4
Reg Anesth (1976)							4	4
Eur J Anaesthesiol (1984)								4
J Cardiothorac Anesth (1987)								6
J Clin Anesth (1988)								4
J Neurosurg Anesth (1988)								4
J Pediatr Anaesth (1990)								4
J Obstet Anaesth (1991)								4
Total	6	10	16	20	36	42	68	98

[a] Issues per year at start of each decade 1922–1992.

with the literature as an author (and editor) should be.

2. Articles that constitute the trivia of our specialty. Yes, the material they report may be valid and even original. These articles serve, nevertheless, merely to fill in the inconsequential interstices of our knowledge—the dotting of *i*'s and crossing of *t*'s. Consider the latest bandwagon in the anesthesiology literature, for example: articles describing yet another volume or yet another concentration of yet another local anesthetic, combined with yet another volume and another concentration of alfentanil, fentanyl, or morphine injected epidurally for relief of pain after cesarean section. The combinations are infinite. How tiresome. Ultimately, how trivial.
3. Articles that address nonquestions and do so often at great cost with stupendously expensive and sophisticated equipment. Something like the effect, for example, of the latest muscle relaxant on middle ear barometric pressure during alfentanil anesthesia.
4. Finally, a close relative of papers posing nonquestions are those that set up straw men to knock them down. A study of this type might be to examine why bronchospasm develops more frequently during desflurane in patients with blue eyes than in patients with brown eyes.

The increase in the frequency of less-than-outstanding articles that has occurred over the years has not taken place suddenly. It has been slow. Insidious. Glacial. So slow, insidious, and glacial as to escape detection, especially in view of the fact that many papers being published are indeed important and meritorious in all respects.

Why this increase in the percentage of articles of limited value appearing in our anesthesiology journals? The genesis of this change is associated with, and not only temporally but causally related to, another phenomenon. This phenomenon consists of a gradual but inexorable increase in the number of anesthesiology journals being published. Consider the hard data in Table 1. This table shows the increase in the number of anesthesiology journals being published between 1922, when the first anesthesiology journal appeared, and 1992. Note particularly the sharp increase since 1970. These data are incomplete. They include only English-language journals, and, even at that, not all English-language journals are included. There are, today, no less than 53 anesthesiology journals in all languages being published worldwide.

Not only has the number of anesthesiology journals increased, so, too, has the number of issues published per year, as shown at the bottom of Table 1 and more graphically in Figure 1.

The recent increase in the number of anesthesiology journals is in turn associated with and causally related to the fact that essentially all of the most recently introduced journals are financially sponsored not by professional societies but by publishing houses. These journals are, therefore, for-profit publications. As such, they have, must have, by definition, goals and perspectives quite different from those of journals sponsored by nonprofit anesthesia societies. They are, for one thing, inevitably under some degree of pressure, however subtle and however indirect, to publish enough articles just to keep going. Such pressure can only weaken the criteria of quality when it comes to deciding

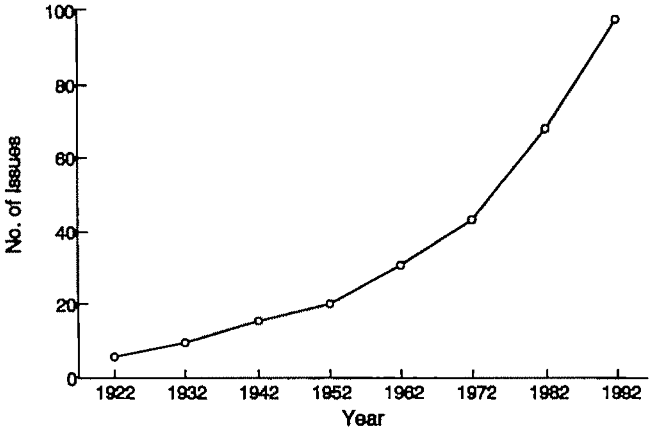

Figure 1. Growth of anesthesiology literature by decade (issues per year at start of decade).

what is or is not publishable. Not that nonprofit journals are immune to such pressure, but the level of pressure and the frequency of trespassing on quality are less.

There must be no question whatsoever about the fact that the worldwide, dramatic increase in anesthesiology itself necessitates an increase in the number of anesthesiology journals. The practice of anesthesia has spread to incorporate new areas. The number of people in anesthesia has increased. So, too, has the amount of research of the highest quality increased, leading to new information. All this is well, good, necessary, and desirable.

But the flip side to this coin is an increase in journal pages available in anesthesia that has increased more than the increase in information that deserves to be published. Again, the latter has indeed increased. No question about that. But it has not increased as much as the increases shown in the accompanying table and figure.

The result of this imbalance between numbers of journal pages available for publication of articles in anesthesia and numbers of materials that deserve to be published, together with the entry of profit-making in anesthesiology journals, is that the good material—the material of importance to all of us—is diluted. The good, the important material is diluted within a given issue of a given journal by materials the need for which is obscure. The good material is even further diluted by being spread amongst so many different anesthesiology journals.

This spreading out of materials worthy of our attention in an increased number of anesthesiology journals and the dilution of those materials worthy of attention within one journal by publication of indifferent materials are the intellectual costs associated with the proliferation of journals both at present and, apparently inevitably, in the future. The result is and will be an impediment to ready access to new information, information that really counts—that is really important, not just publishable, but important. This is a situation with a real potential for eroding the very foundations of anesthesiology as a respected academic, intellectual, and professional discipline of the first rank purely and simply because it undermines the quality of the written word.

What can be done about this situation? Certainly the number of anesthesiology journals cannot be cut back. Nor can the introduction of new journals be prevented. Freedom of press, etc. What can, and must be done, however, is for all anesthesiologists—trainees and staff, private practitioners and faculty alike—to recognize the reality of this situation and its attendant educational dangers and to change—radically—how we go about the acquisition of knowledge. We cannot try to avoid the situation by reliance on journals that consist mainly of review articles. Such predigested material at best only spoon-feeds the reader. Nor can we rely on panels and lectures for the promulgation of information that is new, important, and valid to anesthesiologists. Panelists and lecturers rarely have to prove the scientific validity of what is said, nor is it peer-reviewed. Reliance solely on panels and lectures for the acquisition of knowledge all anesthesiologists need verges on the acquisition of knowledge by gossip.

Now and in the future, we must change in five ways our attitudes, our practice, and our approach to keeping up with what goes on in this world anesthetically, a prime responsibility no matter where or how one practices.

First, we must continue to rely on the written word as presented in peer-reviewed anesthesiology journals if we are to keep abreast of what is new, important, and valid.

Second, we must learn and we must teach others, especially residents, the need to systematically develop and to refine an acute sense of discrimination when reading published articles, today even more than in the past. The art of discrimination is not learned by passive osmosis any more than any other art is. Program directors and residency-accrediting committees should require that trainees be exposed to a systematic series of structured lectures on how to separate wheat from chaff when going over today's written word in the anesthesiology literature. Such a program would surely be of as much value to teachers as to trainees.

Third, we should all—residents and practitioners alike—become resigned to the fact that it will take twice as long and take twice as much effort to keep abreast of things that count as it did in the past, because we now have twice as many journals to read.

Fourth, we must all also resign ourselves to the fact that keeping up to date will also be at least twice as expensive: we have to subscribe to twice the number of journals to get the same amount of worthwhile information we could get in the past.

Finally, trying to avoid the problem by hiding within a sub-subspecialty, e.g., learning more and more about less and less, is not acceptable. To do so may decrease the number of journals and articles one needs to read. Our patients do not come to us, however, with only sub-subspecialty disease. We must care for the entire patient, not just part of him or her. We must stay abreast of what goes on in areas outside our area of special interest within anesthesiology if we are to be truly expert in a specialty as uniquely transdisciplinary as anesthesiology.

Anesthetic Management for Magnetic Resonance Imaging: Problems and Solutions

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Basic Principles of Magnetic Resonance Imaging
Magnetic Field Problems
  Implanted Objects
  Propelled Objects
  Noise
  Radio Frequency Heating
  Occupational Exposure
  Monitor Interference
Monitors and Equipment
  Electrocardiography
  Pulse Oximetry and Peripheral Perfusion
  Blood Pressure
  Anesthesia Machines
  Respiratory Gas Analysis
  Intravenous Infusion Pumps
  Specialized Equipment
Patient Problems
  Patient Accessibility
  Hypothermia
  Miscellaneous Problems
Anesthetic Techniques
  Monitored Anesthesia Care
  General Anesthesia
    Pediatric
    Adult
Conclusion

Magnetic resonance imaging (MRI) involves use of high-strength magnetic fields to provide digitalized tomographic imaging of the body. Anesthesiologists are sometimes involved in patient care because quality of the image depends in part on the patient remaining immobile. Patient monitoring and anesthetic management are challenging because the high magnetic fields interfere with electronic monitors and ferromagnetic components of common equipment (1). Noise, propelled ferromagnetic objects, access to the patient, and airway management are a few additional problems created by the MRI environment. The following is an overview of the literature and will suggest solutions to the problems encountered with anesthesia for MRI.

Field strengths utilized vary from institution to institution but are generally in the 0.15 Tesla (T) to 2.0 T range (2). The total scanning time typically requires about 1.5 h.

Magnetic resonance imaging is superior to computed tomography for neurologic and soft tissue examination (3). Structures within the cranium, spinal column, and pelvis are delineated with high contrast (4). As a diagnostic tool, MRI may be used for follow up of intracranial lesions and for stereotaxic guidance during intracranial surgery (5,6). Magnetic resonance imaging is well suited for mediastinal and pericardial examinations as it can easily distinguish between fat, vessels, and tumor (4). Airway anatomy can be assessed in cases of suspected or proven difficult intubations or an abnormal epiglottis (7,8). Magnetic resonance imaging may be a primary diagnostic tool for aortic disease (1). Oncologic hyperthermia is possible using the magnetic fields of MRI to increase *local* tissue temperature (9,10).

Basic Principles of Magnetic Resonance Imaging

The Tesla is a measure of the strength of a magnetic field (1 Tesla = 10,000 gauss [G]). The earth's magnetic field is 5×10^{-5} T (11). The MRI magnet is a liquid nitrogen cooled superconductor, cooled to 4°K, producing up to a 2.0-T magnetic field. Because 72–96 h may be required to reestablish the magnetic field, it is deactivated only in an emergency.

Atoms with net electrical charges (those having an odd number of protons and/or neutrons in their nuclei) have intrinsic magnetic properties that enable an extrinsic static magnetic field to align them and induce precessional rotation parallel to this field (2,4). The atoms are then subjected to a radio frequency (RF) pulse that deflects the orientation of the atoms. As the RF pulse is removed, the nuclei rotate back into alignment with the static magnetic field. As these

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nuclei "relax," the energy released is used to create the MRI image. Hydrogen is the atom most often used for imaging; it is present in tissue as mobile water and immobile long chain triglycerides. Because of different chemical environments, the relaxation rates vary for specific body tissues, especially water and fat, allowing for differentiation of body structures.

Magnetic Field Problems

Implanted Objects

Problems with a variety of implanted ferromagnetic objects have been included in numerous reports (11–16). Patients with artificial pacemakers should be excluded from MRI studies because of pacer inactivation or conversion to an inappropriate mode by closure of the reed switch. A field of 17 G can convert some pacers to the asynchronous mode (16). Torque on the pacer itself or voltage induction across the pacing leads may lead to disconnection, discomfort, or microshock. In a 1.5-T field all multiple types of pacers failed (17).

As little fibrosis occurs in the central nervous system, aneurysmal clips may be detached intracranially with disastrous consequences (14). Heating of implanted nonferromagnetic prostheses has not proven to be a problem, and these patients may be able to undergo MRI without incident (11,18). An unusual complication of MRI is eye damage secondary to retinal hemorrhage from an unknown imbedded metallic object (14). Other implants of importance include cochlear and stapedial implants, although these are usually stainless steel. Heart valves implanted in recent years are not ferromagnetic, and flow changes or heating are not significant problems (14). Cosmetic tattoos with metallic dyes have been associated with local irritation. Certain metallic eye make-ups have led to eye and periorbital irritation (14,19).

To avoid or detect these problems with implanted objects, the anesthetist should move the patient slowly into and out of the field before induction and respond quickly to any reported sensations (14).

Propelled Objects

Vigilance and caution must be used to prevent injury to patients, personnel, and equipment from propelled ferromagnetic objects. Monitors and other necessary equipment must be secured. They may be bolted to floors and walls or kept distant from the magnetic field. Care must be taken to search personal attire for pens, needles, vials, scissors, and other objects that are ferromagnetic. Patients should also be carefully searched for ferromagnetic objects. Restraining straps, pins, and other medical devices may cause patient injury (20). Some reports have suggested placing a line on the floor at the 50-G line to alert personnel to the increased danger of propelled objects (14).

Beryllium tools are useful in MRI. However, hands must be washed after handling because beryllium metallic dust is a pulmonary toxin (14). Safe metals include nickel, stainless steel, alloys, tantalum, and titanium (19). It is a good idea to install a "test" magnet outside the scanner room to detect potential ferromagnetic objects (14).

Noise

The noise from the MRI scanner is due to torque on loops of wire which have gradient currents induced in them during the RF pulses. This causes vibration and therefore audible noise, hampering communication and making assessment of cardiac and respiratory function virtually impossible using standard acoustic precordial or esophageal stethoscopes. Ear plugs for pediatric patients and earphones with music for adults are used to decrease noise exposure. Noise during scans may average 95 decibels in a 1.5-T scanner (14). Permissible exposure to noise of this level should be limited to 2 h/day (14).

Radio Frequency Heating

Although no clinical signs of *core* body heating have been reported with MRI, RF heating from induced currents is a potential problem especially with field strengths greater than 2 T (13,14). A measure of this heating is specific absorption rate. The FDA limit is 0.4 W/kg averaged over the whole body. The main concerns occur with field strengths greater than 2 T (14). Specific absorption rate may be reduced by changing the pulse sequence, decreasing the number of slices, lengthening the repeat time, decreasing the RF scale, and switching to a smaller transmitter coil. Ex vivo temperature measurements of large metal prostheses have not demonstrated heating in fields 6.4 times that experienced in MRI (14,18).

Occupational Exposure

Magnetic resonance imaging does not require ionizing radiation, and there are no reports of harm from tissue contact with the magnetic fields (4). Although no oncologic or genotoxic effects have been found, caution is advised during pregnancy, especially during the first trimester (21–24). The FDA has not established limits on total MRI exposure. Local exposure levels, however, are mandated: the field strength is limited to 2 T, with time varying fields less than 3 T/s. Radio frequency must be limited to 2 W/kg over 1 g of tissue and 0.4 W/kg averaged over the whole body (19). Mice exposed over multiple generations to 1.89 T for 2 yr failed to reveal any specific damage (21). Cells exposed to 2.7 T for 17 h have not shown aberrations (22,23). A study of 792 workers exposed with field strengths of 0.5 mT to 2 T did not show increases in 19 disease categories (24). No alterations of cardiac or neurologic function have been reported in field strengths up to 7 T (13,14). Magnetophosphenes causing visual sensations such as light flashes or flickers have been reported in magnetic field changes of 1.3 T/s (25).

Monitor Interference

Electron beams are affected by the static magnetic field, which distorts and displaces the image on monitors and other cathode ray displays. This requires the anesthetist to find a point of least distortion by orienting the monitor in various positions relative to the magnetic field. Most electrocardiographic artifact cannot be eliminated, and monitors used should have good artifact suppression characteristics (3).

Monitors themselves can disturb the signal/noise ratio of the MRI. Electrical connections to the patient act as antennas and introduce RF signals that can distort the MRI image (3,11). Magnetic fields created by the electronics within the monitors can disturb the MRI image.

Monitors and Equipment

Monitors and equipment are listed as described in the original papers. Monitors acceptable in low-strength magnetic fields may not provide useful information in the new high strength magnetic fields used today (1).

Electrocardiography

Electrocardiography (ECG) introduces problems with both image degradation from wire leads acting as antennas and the inability of the ECG monitor to discern the ECG from the background static magnetic field and RF pulses. A reported trial of telemetric and fiberoptic ECG transmission stated that RF pulsing caused severe artifact (11). Voltage induced in the wire leads may pose burn and electrical shock hazards to the patient (3). Acceptable monitors are reported in Table 1.

Table 1. Electrocardiography Devices Reported Acceptable

Author	Field strength (T)	Device	Reference
Roth	0.15	Hewlett-Packard 78 100A Telemetry Waltham, Mass. Saturn Monitor Space Lab, Inc. Chatsworth, Calif.	11
Barnett	0.6	Model 78100 A Hewlett-Packard Palo Alto, Calif.	36
Groh	1.0	Sirecust 404	39
Dimick	1.5	Hewlett-Packard Waltham, Mass.	26
Karlik	1.5	HP 7830	30
Rao	1.5	Astro-Med DashII	28
Patteson	2.0	ARS V-52 Tokyo, Japan	

Dimick reported obtaining a 12-lead ECG in a 1.5-T machine and studied optimal electrode placement. Leads V_5 and V_6 maximized QRS and minimized artifact (26). Placing ECG electrodes in a single line close together was reported acceptable for monitoring (3). Additional suggestions for improving ECG monitoring include twisting cables, keeping electrodes close together, positioning electrodes near the three-dimensional center of the imager, and maintaining the plane of any loop of cable parallel to the magnetic field lines (27). Nonferromagnetic fasteners and electrodes (NDM 01-5010, NDM Corp., Dayton, Ohio) do not interfere with the MRI (27). Graphite and copper cables with plastic springs (BR611U, Nihon-Kohden America Inc., Irvine, Calif.) and NDM ECG leads (NDM Corp.) do not affect the MRI image (11,27).

A 7–10-Hz filter may reduce artifact in most electrocardiography leads (28). Low-pass filters are incorporated into some commercial monitors (HP 78110A/78101A, Hewlett-Packard, Waltham, Mass.) (27). A "gated" ECG signal may be obtained by subtraction of the MRI field and RF pulses from the ECG signal obtained, leaving the net patient ECG signal (29). Most recent MRI imagers contain ECG monitoring to provide gated cardiac images (30). Scan gating, timed to the R wave of the ECG, will prolong the MRI study depending on heart rate.

T-wave changes have been reported in fields greater than 0.3 T, presumably because of alterations in regional blood flow perpendicular to the magnetic field (12). There does not appear to be any significant physiologic change due to the T-wave alterations (12–14,26).

Table 2. Oximetry Monitoring Devices Reported Acceptable

Author	Field strength (T)	Device	Reference
McArdle	0.6	Nellcor N-100 Haywood, Calif. Ohmeda Biox 3700 Madison, Wis.	33
Groh	1.0	Drager-Nellcor	39
Karlik	1.5	Ohmeda Biox 3700	30
Rao	1.5	Biochem 1040	28
Patteson	2.0	Criticare System 501+ Pewaukee, Wis.	

Table 3. Doppler Monitoring Devices Reported Acceptable

Author	Field strength (T)	Device	Reference
Roth	0.15	Parks Medical 811 Parks Medical Beaverton, Ore.	11
McArdle	0.6	811 Ultrasonic Doppler Parks Medical Beaverton, Ore. Hewlett-Packard 8813A Mountain View, Calif.	33
Rao	1.5	Parks Medical 811	28
Shellock	1.5	Medpacific LD 5000 Seattle, Wash.	32
Patteson	2	Parks Medical 806-CA Beaverton, Ore.	

Table 4. Blood Pressure Monitoring Devices Reported Acceptable

Author	Field strength (T)	Device	Reference
Sellden	0.02	Dinamap 1846 Critikon Ltd., Tampa, Fla.	44
Nixon	0.5	Dinamap	12
Rejger	0.5	Accutorr, Datascope Noevelaken, The Netherlands	3
Barnett	0.6	Spacelab 414 Opt21 Hillsboro, Ore. DTX Transducer Gould Oxnard, Calif.	36
Groh	1	Dinamap	39
Karlik	1.5	Dinamap 1846 SK/P Critikon Inc., Tampa, Fla.	30
Shellock	1.5	Omega 1400 Invivo Research Broken Arrow, Okla.	32
Smith	1.5	Accutorr 2A Datascope Corp. Paramus, N.J.	20
Patteson	2.0	Dinamap 8100 Critikon, Inc. Tampa, Fla.	

Pulse Oximetry and Peripheral Perfusion

Various oxygen saturation monitors have been found useful and provide information regarding pulsatile peripheral blood flow and oxygenation. These monitors are susceptible to interference from the changing magnetic field and will occasionally be briefly deactivated by RF pulses. Most monitors may be placed within 2 m of the magnet, but greater distances provide longer periods of uninterrupted function. The probe is placed on a distal extremity as far from the scan site as possible, but severe burns to a finger caused by gradient or RF magnetic fields induced in a loop of wire from a pulse oximeter probe have been reported (31). Oximeters reported acceptable are listed in Table 2.

Plethysmography can provide a waveform from a distal extremity that correlates with pulsatile perfusion (29,32). Higgins et al. (29) describes using a Cardioloine III Pulsorette in a 0.35-T field. At the author's institution, a Hewlett-Packard HP 78330A (Waltham, Mass.) monitor is used with the probe placed on the large toe. This monitor, along with pulse oximetry, provides evidence of pulsatile perfusion.

Pulsatile blood flow through the dorsalis pedis, radial artery, ear lobe, and lips can be acoustically monitored via Doppler probes (11,32,33). Doppler monitoring devices reported acceptable are listed in Table 3. Dopplers may require use of headphones as audio output is hampered by noise during the RF pulses.

Blood Pressure

Blood pressure monitoring during MRI can be accomplished using the oscillometric method, which is particularly immune to electromagnetic interference (12,32). Monitors that provided accurate measurement of blood pressure during MRI are reported in Table 4. Monitors may be equipped with extended tubing and plastic connectors and are usually placed as far from the magnet as possible.

Fiberoptic systems and invasive pressure measurements obtained with long pressure lines have been used to monitor arterial oxygenation and blood pressure (12,32,34,35). Transducers reported to be MRI-compatible include Steridome model 043279-999 (Cobe Monitoring, Lakewood, Col.) and DTX Gould (Gould Inc., Oxnard, Calif.) (35,36). Fiberoptics, placed through an 18-gauge catheter into a femoral artery in a cat, are reported to give measurements of blood pressure and cardiac activity. The report did not state the strength of the magnetic field (34).

Table 5. Anesthesia Machines/Ventilators Reported Acceptable

Author	Field strength (T)	Device	Reference
Boutros	NA	Mapleson D 5116W Vital Signs Totowa, N.J.	40
Andoh	0.15	Boyce International 2 Model B	6
Nixon	0.5	Monaghan 225	12
Rejger	0.5	Laerdal N-4001 Mapleson D Stavanger, Norway Oxylog Drager	3
Barnett	0.6	Monaghan 225	36
Groh	1.0	Siemens 900 C Servo Iselin, N.J.	39
Karlik	1.5	Boyle MS-222 Ohmeda, Madison, Wis. Airshield Ventimeter II Air-Shield Hatboro, Pa. Monaghan 225 Monaghan Medical Plattsburg, N.Y.	30
Mirvis	1.5	Siemens 900 C Iselin, N.J.	38
Rao	1.5	Narco Airshield VC 20-1	28
	1.5	Ohmeda (R) Excel 210	37
Smith	1.5	225/SIMV Monaghan Med Plattsburg, N.Y.	20
Patteson	2.0	Mapleson D. Dryden Corp Indianapolis, Ind.	

Anesthesia Machines

There are several reports describing use of anesthesia machines near MRI scanners. Considerations include (a) no danger to the patient; (b) proper function in the magnetic field; and (c) no effect on the MRI image (6). Breathing circuits and anesthesia machines utilized in magnetic fields are listed in Table 5. Some machines are bolted to the walls and others are modified by removal of ferromagnetic components (11,28,37). Aluminum cylinders replace ferromagnetic ones on the anesthesia machines. Some specially engineered "MRI compatible" ventilators are available. They are pneumatically driven, fluidic-controlled, and volume-cycled (20,34). These machines include the 225 SIMV (Monaghan Medical Corp., Plattsburg, N.Y.) and the Narco Airshield VC 20-1; they have been found to be functional in a 1.5-T field (20,28). The use of a Siemens-Elema 900C (Siemens-Elema Ab, Iselin, N.J.) ventilator has been reported in a 1.5-T machine (38). The limiting feature on this ventilator is the PEEP valve, which is a solenoid type and must be at least 1.2 m away from the magnet bore (38). Anesthesia in a 1-T field has been maintained using inhalational agents with a Siemens 900 C Servo machine (39). Pressurized oxygen must be supplied to power these machines.

The use of a long Mapleson D circuit provides oxygenation and ventilation for the patient undergoing MRI. This circuit is lightweight, portable, flexible, and provides tactile sensation regarding the patient's airway and ventilation. It is also useful during transportation (40). Mapleson D circuits allow transport of patients into the MRI suite from the scanner lobby after induction with anesthesia machines that contain ferromagnetic components. Oxygen may be supplied from plastic cannisters containing liquid oxygen (Penox Technologies, Pittston, Pa.).

Respiratory Gas Analysis

Respiratory gas analysis and capnography allow the anesthesiologist to monitor patient ventilation, circuit integrity, and anesthetic gas concentrations. Devices may be interfaced to the patient with extended plastic tubing. This does not decrease monitor sensitivity (41). Monitors found functional in MRI fields are listed in Table 6. Oxygen analyzers are essential in monitoring gases delivered by anesthesia machines. Infrared monitors analyzing end-tidal carbon dioxide will give rapid detection of loss of ventilation and circuit disconnection (12,32). Chest wall movement has been detected using a chest bellows and apnea alarm mattress (11,12). Fiberoptic monitoring of respiratory motion is possible with esophageal, intraperitoneal, rectal, and bronchial probes (34).

Intravenous Infusion Pumps

Infusion pumps may be nonfunctional or inaccurate in MRI fields (14,15). Medications infused through drips without pumps are subject to inaccurate dosages. Total intravenous anesthesia is most easily managed with infusion pumps (3). Devices found accurate and functional in a magnetic field are listed in Table 7. It is important to remember that pumps must be supported on nonferromagnetic poles. When rapid infusion of fluids is required, plastic disposable pressure bags (Infusable IN-8000, Biomedical Dynamics, Minneapolis, Minn.) may be used.

Specialized Equipment

Some investigators describe use of plastic precordial (Argyle, Sherwood Medical, St. Louis, Mo.) and esophageal stethoscopes. These may not be acceptable monitors when used by themselves as all audible

Table 6. Gas Analysis/Capnography Devices Reported Acceptable

Author	Field strength (T)	Device	Reference
Nixon	0.5	Engstrom Eliza	12
Rao	0.5	Ohmeda 5120	28
Rejger	0.5	Multicap Datex Medical Electronics Hoevelaken, The Netherlands	3
Karlik	1.5	Puritan-Bennett 222 Wilmington, Mass.	30
Shellock	1.5	Tri-med 511G Biochem International Milwaukee, Wis.	32
		515 Respiration Monitor Biochem International Waukesha, Wis. 8800 Capnometer Biochem International Waukesha, Wis.	41

Table 7. Intravenous Infusion Devices Reported Acceptable

Author	Field strength (T)	IV pump	Reference
Engler	0.28	IVAC 530	15
Rejger	0.5	WTI SP 102U Adquipment Rotterdam, The Netherlands	3
Karlik	1.5	Fenwal Baxter Corp. Deerfield, Ind. IVAC 530	30

input from these monitors is obscured by scanner noise. Their use is advocated for backup should other monitors fail and for verification of cardiac and respiratory sounds during quiet periods in the scanning process.

Plastic laryngoscopes (North American Medical; PT#6001, Loudonville, N.Y.) are available; however, the batteries in the handle still cause a pull from the magnetic field (12,42). Laryngoscopes have been modified to operate directly from a 5-V DC source connected to the MRI machine. An 8-ft cable with nonmagnetic BNC connectors is used to connect the laryngoscope to the power source (30). Various specialized alternatives to other monitors are described in their respective sections.

Patient Problems

Patient Accessibility

The patient's distance from the anesthetist creates problems with airway management, intravenous access, patient visualization, and monitor application (43). If unintentional extubation occurs, it may be necessary to discontinue the scan and remove the patient to the foot of the scanner bed. It is possible and sometimes necessary for personnel to position themselves within the scanner coil to evaluate the airway during a scan. A quick release table is used for rapid extrication of the patient. With the patient removed from the MRI tube, laryngoscopy at the foot of the magnet bore is possible in emergency situations with plastic laryngoscopes.

Because of the anesthetist's distance from the patient in the MRI tube, extensions must be placed on intravenous lines. In the pediatric population, this increased line distance may add to the fluid volume infused when administering injections.

Table 8. Temperature Monitoring Devices Reported Acceptable

Author	Field strength (T)	Device	Reference
McArdle	0.6	Yellow Springs Temp Module Yellow Springs, Ohio Mon-A-Therm St. Louis, Mo.	33
Karlik	1.5	Yellow Springs Yellow Springs, Ohio	30

Hypothermia

Care must be taken to avoid hypothermia in all patients, especially in the pediatric population. Air flow directed through the scanner cavity increases heat loss, making hypothermia a distinct problem. Warmed fluid packs such as bags of warm intravenous fluids, heating pads, single-use thermal packs (Portawarm #11475-010, Baxter Pharmaseal, Moberly, Mo.), airway humidification, and covering the patient are methods to minimize heat loss. Rectal temperature probes have been used to monitor temperature in 0.6-T fields (30,33). Table 8 lists acceptable monitors. Nonferromagnetic disposable temperature strips (Stat Temp, Trademark Corp, Fenton, Mo.) may be used.

Miscellaneous Problems

Claustrophobia has been reported in up to 7% of awake patients (12). Obesity may limit physical placement of the patient into the magnet bore, as well as decrease space available for access to the patient, airway, and monitor attachments (13). Bank cards, credit cards, pagers, and digital watches may suffer erasure or alteration of stored information.

Anesthetic Techniques

Many techniques have been described that include some or all of the principles described. Newer drugs such as oral midazolam, used in the pediatric population, have made the anesthetic management of children somewhat easier. Anesthesia can be safely achieved if drug delivery and patient monitoring are applied with knowledge of the effects of magnetic fields.

Monitored Anesthesia Care

Consideration should always be given to use of monitored anesthesia care. Pediatric, anxious, or confused patients may remain immobile for MRI scanning with appropriate medication. Monitoring that would routinely be available for general anesthesia under the same circumstances should be applied. McArdle et al. (33) described the use of oral chloral hydrate (75 mg/kg) for sedation in a term infant. Oral midazolam (0.5–0.75 mg/kg) has also been advocated for sedation in children. In adults, intravenous access is more easily established and many medications, such as midazolam and fentanyl, are available for sedation.

General Anesthesia

Many patients cannot be safely sedated for MRI and therefore require general anesthesia. Pediatric and adult patients present the same considerations for anesthesia in the MRI suite as they would in the operating room. Inhalation inductions are more likely to be required (or requested) in the pediatric population. Inductions of anesthesia in the lobby of the MRI suite distant from the magnetic field may allow use of a familiar anesthesia machine. Total intravenous anesthesia may be maintained once intravenous access is obtained. The patient is then transported into the MRI field on a nonferromagnetic stretcher.

Pediatric. Many techniques have been described in pediatric patients. Rejger et al. (3) described induction in an adjacent induction room. Manual ventilation was then maintained for children under 3 yr of age. Geiger and Cascorbi (42) described oral premedication with diazepam followed by intramuscular methohexital. Anesthesia was then continued with intravenous agents and spontaneous respiration. Boutros and Pavlicek (40) used inhalation induction and obtained intravenous access followed by intubation. Anesthesia was maintained with ventilation using a Mapleson D circuit, 100% oxygen, and incremental thiopental. Sellden et al. (44) obtained intravenous access, then utilized premedication with midazolam (0.2 mg/kg IV) followed by induction with atropine (0.01 mg/kg), thiopental (5 mg/kg), pancuronium (0.1 mg/kg), fentanyl (2 μg/kg), and nasal intubation. Intramuscular ketamine may be used for sedation or induction before intravenous access.

Adult. Numerous techniques are described for adults. Rafferty et al. (45) used a laryngeal mask airway as an adjunct to airway maintenance and support. Rejger et al. (3) utilized continuous total intravenous anesthesia supported by mechanical ventilation or spontaneous respiration after induction in an adjacent room. Smith et al. described total intravenous anesthesia using thiopental, narcotic, muscle relaxant, and mechanical ventilation. Induction and intubation occur outside the scanner's magnetic field. Nasal intubation may provide a more secure airway than does oral intubation within the scanner confines. Many different safe techniques may be devised around available monitors and equipment.

Conclusion

Problems created by the magnetic field have been presented along with possible solutions. Awareness of specific risks associated with anesthesia for MRI should temper its usage in patients requiring general anesthesia. As medications evolve and as technology enhances our monitoring ability, anesthesia in MRI will likely become more commonplace and more easily and safely managed.

References

1. Messick JM, MacKenzie RA, Nugent M. Anesthesia at remote locations. In: Miller RD, ed. New York: Churchill Livingstone, 1990:2061–88.
2. Baker HL, Berquist TH, Kispert DB, Reese DF, Houser OW. Magnetic resonance imaging in a routine clinical setting. Mayo Clin Proc 1985;60:75–90.
3. Rejger VS, Cohn BF, Vielvoye GJ, Raadt FB. A simple anaesthetic and monitoring system for magnetic resonance imaging. Eur J Anaesthesiol 1989;6:373–8.
4. Cahalan MK, Litt L, Botvinick EH, Schiller NB. Advances in noninvasive cardiovascular imaging: implications for the anesthesiologist. Anesthesiology 1987;66:356–72.
5. Carsin M, Rolland Y, Gandon Y, Gagey N, Brassier G, Simon J. Contribution of RMI to the diagnosis and posttherapeutic monitoring of brain stem tumors. J Neuroradiol 1990;17:50–9.
6. Andoh K, Ohkoshi T, Odagiri K, Kyuma Y, Hayashi A. Technical note: enhanced MR-guided stereotaxic brain surgery with the patient under general anesthesia. AJNR 1991;12:135–8.
7. Hotchkiss RS, Hall JR, Braun IF, Schisler JQ. An abnormal epiglottis as a cause of difficult intubation—airway assessment

using magnetic resonance imaging. Anesthesiology 1988;68: 140–2.
8. Schneider M, Probst R, Wey W. Magnetic resonance imaging—a useful tool for airway assessment. Acta Anaesthesiol Scand 1989;33:429–31.
9. Delannoy J, LeBihan D, Hoult DI, Levin RL. Hyperthermia system combined with a magnetic resonance imaging unit. Med Phys 1990;17:855–60.
10. Dickinson RJ, Hall AS, Hind AJ, Young IR. Measurement of changes in tissue temperature using MR imaging. J Comput Assist Tomogr 1986;10:468–72.
11. Roth JL, Nugent M, Gray JE, et al. Patient monitoring during magnetic resonance imaging. Anesthesiology 1985;62:80–3.
12. Nixon C, Hirsch NP, Ormerod IEC, Johnson G. Nuclear magnetic resonance. Its implications for the anaesthetist. Anaesthesia 1986;41:131–7.
13. Consensus Conference. Magnetic resonance imaging. JAMA 1988;259:2132–8.
14. Gangarosa RE, Minnis JE, Nobbe J, Praschan D, Genberg RW. Operational safety issues in MRI. Magn Reson Imaging 1987; 287:292.
15. Engler MB, Engler MM. The effects of magnetic resonance imaging on intravenous infusion devices. West J Med 1985;143: 329–32.
16. Pavlicek W, Geisinger M, Castle L, et al. The effects of nuclear magnetic resonance on patients with cardiac pacemakers. Radiology 1983;147:149–53.
17. Erlebacher JA, Cahill PT, Pannizzo F, Knowles JR. Effect of magnetic resonance imaging on DDD pacemakers. Am J Cardiol 1986;57:437–40.
18. Davis PL, Crooks L, Arakawa M, McRee R, Kaufman L, Margulis AR. Potential hazards in NMR imaging: heating effects of changing magnetic fields and RF fields on small metallic implants. AJR 1981;137:857–60.
19. Scherzinger AL, Hendee WR. Basic principles of magnetic resonance imaging—an update. West J Med 1985;143:782–92.
20. Smith DS, Askey P, Young ML, Kressel HY. Anesthetic management of acutely ill patients during magnetic resonance imaging. Anesthesiology 1986;65:710–1.
21. Osbakken M, Griffith J, Taczanowsky P. A gross morphologic, histologic, and blood chemistry study of adult and neonatal mice chronically exposed to high magnetic fields. Magn Reson Med 1986;3:502–17.
22. Wolff S, James TL, Young GB. Magnetic resonance imaging: absence of in-vitro cytogenetic damage. Radiology 1985;155: 163–5.
23. Geard CR, Osmak RS, Hall EJ. Magnetic resonance and ionizing radiation: a comparative evaluation in vitro of oncogenic and genotoxic potential. Radiology 1984;152:199–202.
24. Budinger TF, Bristol KS, Yen CK. Biological effects of static magnetic fields. Abstracts of the Society of Magnetic Resonance in Medicine, New York, 1984:113.
25. Budinger TF, Cullander C, Bordow R. Switched magnetic fields thresholds for the induction of magnetophosphenes. Abstracts of the Society of Magnetic Resonance in Medicine, New York, 1984:118.
26. Dimick RN, Hedlund LW, Herfkens RJ, Fram EK, Utz J. Optimizing electrocardiographic electrode placement for cardiac-gated magnetic resonance imaging. Invest Radiol 1987;22: 17–22.
27. Wendt RE, Rokey R, Vick GW. Electrocardiographic gating and monitoring in NMR imaging. Magn Reson Imaging 1988; 6:89–95.
28. Rao CC, McNiece WL, Emhardt J, Krishna G, Westcott R. Modification of an anesthesia machine for use during magnetic resonance imaging. Anesthesiology 1988;68:640.
29. Higgins CB, Lanzer P, Strak D, et al. Imaging by nuclear magnetic resonance in patients with chronic ischemic heart disease. Circulation 1984;3:523–1.
30. Karlik SJ, Heatherley T, Pavan F, Stein J, Lebron F, Rutt B. Patient anesthesia and monitoring at a 1.5-T MRI installation. Magn Reson Med 1988;7:210–21.
31. Shellock FG, Slimp GL. Severe burn of the finger caused by using a pulse oximeter during MR imaging. AJR 1989;153:1105.
32. Shellock FG. Monitoring during MRI. Med Elec 1986;Sept: 93–7.
33. McArdle CB, Nicholas DA, Richardson CJ, Amparo EG. Monitoring of the neonate undergoing MR imaging: technical considerations. Radiology 1986;159:223–6.
34. Legendre JP, Misner R, Forester GV, Geoffrion Y. A simple fiber optic monitor of cardiac and respiratory activity for biomedical magnetic resonance applications. Magn Reson Med 1986;3:953–7.
35. Roos CF, Carroll FE. Fiber-optic pressure transducer for use near MR magnetic fields. Radiology 1985;156:548.
36. Barnett GH, Ropper AH, Johnson KA. Physiological support and monitoring of critically ill patients during magnetic resonance imaging. J Neurosurg 1988;68:246–50.
37. Rao CC, Brandl R, Mashak JN. Modification of Ohmeda (R) Excel 210 anesthesia machine for use during magnetic resonance imaging. Anesthesiology 1988;68:640–1.
38. Mirvis SE, Borg U, Belzberg H. MR imaging of ventilator-dependent patients: preliminary experience. AJR 1987;149: 845–6.
39. Groh J, Weber W, Baierl P, Seiderer M, Peter K. Anaesthesie zur magnetresonanz-tomographie. Anaesthesist 1988;37: 384–6.
40. Boutros A, Pavlicek W. Anesthesia for magnetic resonance imaging. Anesth Analg 1987;66:367–74.
41. Shellock FG. Monitoring sedated pediatric patients during MR imaging. Radiology 1990;177:586–7.
42. Geiger RS, Cascorbi HF. Anesthesia in an NMR scanner. Anesth Analg 1984;63:622–3.
43. Nixon C. Magnetic resonance imaging. Can Anaesth Soc J 1991:420.
44. Sellden H, DeChateau P, Ekman G, Linder B, Saaf J, Wahlund L. Circulatory monitoring of children during anaesthesia in low-field magnetic resonance imaging. Acta Anaesthesiol Scand 1990;34:41–3.
45. Rafferty C, Burke AM, Cossar DF, Farling PA. Laryngeal mask and magnetic resonance imaging. Anaesthesia 1990;45:590–1.

Clinical Use of Magnesium Infusions in Anesthesia

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Magnesium sulfate ($MgSO_4$) has been used for many years on an empirical basis for the control of convulsions in patients with preeclamptic toxemia. Recent interest in the cardiovascular pharmacology of magnesium has led to an examination of the powerful interactions between this agent and the pharmacologic and physiologic mechanisms of hemodynamic control (1). This review examines some aspects of the pharmacology of hypermagnesemia that may be of relevance in anesthesia.

Magnesium is of importance to anesthetists for several reasons. First, the ion is essential for many biochemical reactions, and its deficiency may produce clinically important consequences during anesthesia or in the intensive care unit. Second, the extensive use of $MgSO_4$ in obstetric practice requires that anesthetists be familiar with the pharmacologic actions of this substance and its interactions with anesthetic agents. Third, magnesium has pharmacologic properties that are only recently being appreciated and that may be of value in certain areas of anesthetic practice.

Biochemistry

Magnesium is the fourth most important cation in the body and the second most important intracellular cation. Magnesium activates approximately 300 enzyme systems, including most of the enzymes involved in energy metabolism. The range of and types of enzymes activated by magnesium and the mechanisms by which the metal is involved have been outlined by Durlach (2). Magnesium is also essential for the production and functioning of adenosine triphosphate (ATP), which is fully functional only when chelated to magnesium. The means by which magnesium and magnesium adenosine triphosphate chelates regulate the most important glycolytic enzymes—hexokinase, phosphofructokinase, aldolase, phosphoglycerate kinase, and pyruvate kinase—are described in detail by Garfinkel and Garfinkel (3). Oxidative phosphorylation is magnesium-dependent, and Aikawa (4) has suggested that magnesium may also regulate this process. Other processes dependent on magnesium include the production of DNA and RNA and protein synthesis (5). The ion is an essential regulator of calcium access into the cell and of the actions of calcium within the cell. Magnesium regulates intracellular calcium levels by activating membrane pumps in the cell that extrude calcium from the cytosol (6) and by competing with calcium for transmembrane channels by which extracellular calcium gains access to the interior of the cell (7). In addition, magnesium competes with calcium for binding sites on protein kinases (8) and influences the calcium-mediated release of transmitter substances (9). Thus, magnesium plays an essential role in the regulation of most cellular functions and may be regarded as the natural physiologic calcium antagonist (10).

Magnesium Deficiency

Hypomagnesemia is common in hospitalized patients, especially those in critical care areas. Magnesium deficiency, especially in combination with hypokalemia, has been associated with several types of arrhythmia that respond to magnesium therapy. The evidence for the involvement of magnesium deficiency in the genesis of these arrhythmias has been extensively reviewed by Seelig (11), although Surawicz (12) believed that the case for a causative role for hypomagnesemia is unproven. Whether or not anesthesia exacerbates the arrhythmic tendency in magnesium-deficient patients has not been studied although Krasner et al. (13) demonstrated that preoperative treatment with oral magnesium protected the heart against arrhythmias in open-heart surgery. It seems likely that anesthetizing such patients in the presence of magnesium deficiency may increase the risk of perioperative arrhythmias, and Krasner (14) and Gambling et al. (15) recommended preoperative correction of magnesium deficits. Respiratory muscle power is impaired by hypo-

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magnesemia, which may also have important consequences for anesthesia and critical care (16). The anesthetic implications of hypomagnesemia have been extensively reviewed recently by Gambling et al. (15) and will not be considered further. It is, however, worth reiterating their advice that the treatment of magnesium deficiency by parenteral administration of magnesium salts should be undertaken before operation.

Pharmacology of Hypermagnesemia

Increased serum magnesium levels are rare in clinical medicine as the ion is relatively poorly absorbed from the gastrointestinal tract (4,17) and the renal elimination of any excess magnesium is extremely rapid (18), the excretion of a magnesium load by the kidney being complete within 4–8 h (19). To produce a significant increase in serum levels for therapeutic purposes (e.g., for the control of preeclampsia) in the presence of normal renal function, magnesium should be given via parenteral routes. Magnesium has a moderately large volume of distribution that approximates the volume of the extracellular space and this, coupled with the rapid renal elimination, means that large initial doses (in the order of 40–60 mg/kg of $MgSO_4$) and continuous infusions (at a rate of 15–30 $mg \cdot kg^{-1} \cdot h^{-1}$) or intramuscular injections are necessary to maintain serum magnesium levels in the generally accepted therapeutic range of 2–4 mmol/L.

Central Nervous System

Magnesium is widely regarded as a central nervous system depressant, largely because of its anticonvulsant properties in gestational proteinuric hypertension. Meltzer and colleagues (20,21) used $MgSO_4$ as a general anesthetic. More recently, however, Aldrete (22) dismissed these claims, suggesting that the anesthetic effect was due to cerebral hypoxia from progressive respiratory and cardiac depression. Provided ventilation is maintained, even very high levels of serum magnesium produce virtually no central nervous system depression (23). Although magnesium does depress neural tissue when applied directly (24), magnesium penetrates the blood-brain barrier poorly, and its level in the cerebrospinal fluid is well controlled probably by an active transport mechanism (25). Even in cases where high levels of serum magnesium have been maintained for several days, cerebrospinal fluid magnesium concentrations are only marginally above normal (26). Magnesium therefore probably does not have major anticonvulsant properties unless the convulsions result from magnesium deficiency. Although small but significant increases in cerebrospinal fluid magnesium concentrations have been demonstrated after magnesium treatment, the most likely explanation for the anticonvulsant action of magnesium in gestational proteinuric hypertension is its powerful cerebral vasodilator action, which reverses the cerebral vasospasm now thought to be the principal cause of the convulsions (27–31). Thompson et al. (32) described a 60% reduction in minimum alveolar concentration of halothane in magnesium-treated rats, which they ascribed to a central effect of the ion although this has not been substantiated.

Peripheral Nervous System

Magnesium primarily affects the peripheral nerves by interfering with the release of neurotransmitter substances at all synaptic junctions, although it has been suggested that it may potentiate the action of local anesthetics (33).

Motor end plate. Magnesium at levels more than 2.5 mmol/L produce a dose-dependent presynaptic inhibition of neurotransmitter release in peripheral nerves. This effect is due to competition with calcium for membrane channels on the presynaptic terminal (34,35). At the neuromuscular junction, magnesium concentrations of 5 mmol/L and more produce significant presynaptic neuromuscular blockade. As a result, magnesium will enhance the action of the nondepolarizing muscle relaxants (36–38) and may precipitate severe muscular weakness in patients with the Lambert-Eaton syndrome or myasthenia gravis (35). However, magnesium does not significantly shorten the onset time of nondepolarizing relaxants (39). The interaction of magnesium with the depolarizing muscle relaxants is less clear. Patients treated with $MgSO_4$ do not demonstrate fasciculations (40), and it is generally assumed that magnesium prolongs the action of depolarizing relaxants as it does those of the nondepolarizing group (37,41). Although prolonged treatment with magnesium may increase the duration of succinylcholine blockade, acute hypermagnesemia does not (42). Baraka and Yazigi (43) found no prolongation of the action of a single dose of succinylcholine in magnesium-treated preeclamptic mothers. Preeclamptic patients may have reduced cholinesterase levels that may produce prolongation of the succinylcholine action but magnesium has no effect on this phenomenon (44). The acute administration of $MgSO_4$ before the use of succinylcholine appears to prevent the release of potassium provoked by the relaxant (43,45). Although magnesium may reduce the incidence and severity of succinylcholine-induced muscle pains and may make succinylcholine usable in those circumstances in which the risks of excessive potassium release currently make the relaxant contraindicated, no clinical use has yet been made of these interactions.

Autonomic nerve terminals. Magnesium exerts a similar although less well-known effect on autonomic ganglia (46) and on vagal nerve terminals (47) to that demonstrated at the motor end plate. Serum magnesium concentrations exceeding 2.5 mmol/L produce progressive inhibition of the release of catecholamines from both adrenergic nerve terminals and from the adrenal medulla. Magnesium at higher levels produces ganglionic blockade (34).

Cardiovascular System

Vessels. Magnesium produces vasodilatation by directly acting on the blood vessels (48) and by interfering with a wide range of vasoconstrictor substances (49). In addition to its direct effects on the vessel wall, raised serum magnesium levels may also reduce peripheral vascular tone by a number of other mechanisms, including sympathetic blockade and inhibition of catecholamine release.

Myocardium. As magnesium is a calcium antagonist, increased levels of magnesium should, theoretically, reduce myocardial contractile force. In the isolated heart, increased concentrations of extracellular magnesium ion produces marked depression of contractile force (50,51). In intact animals and humans, the evidence for cardiac depression by clinically useful levels of hypermagnesemia is less clear. Bristow et al. (52) demonstrated an increase in central venous pressure in the intact dog after the intravenous injection of magnesium; and in the same species, Charbon (53) found decreasing ventricular power with successive intravenous injections of $MgCl_2$ using an open-chested model. Aldrete et al. (54) reported a raised central venous pressure in awake dogs at a serum magnesium level of 7 mmol/L, and Critelli et al. (55), using systolic time intervals in human subjects, found decreased myocardial performance after a bolus of 2.5 g of $MgSO_4$. Wallis et al. (56) reported severe myocardial depression with combinations of magnesium and diltiazem but not with magnesium alone. Other studies have failed to demonstrate any myocardial depression and several authors, using magnesium infusions in intact awake sheep (57), anesthetized ventilated baboons (58), and pregnant humans (59), have reported an increase in cardiac output associated with raised serum magnesium levels.

Cardiac rhythm. On the isolated heart, magnesium produces a bradycardia. However, in the intact subject, the inhibition of vagal acetylcholine release produced by magnesium overrides the intrinsic slowing, and a mild tachycardia commonly occurs (47,60). Magnesium is effective in treating a variety of serious arrhythmias, including ventricular arrhythmias resistant to proven antiarrhythmic agents (61). Magnesium is as effective as propranolol and more effective than verapamil in controlling the arrhythmias associated with adrenaline administration (62) and may protect against bupivacaine-induced arrhythmias (63).

Respiratory System

Magnesium has no effect on central respiratory drive, and its only respiratory-depressant effect is due to the neuromuscular block that it produces. It is, however, an effective bronchodilator (64,65), and its successful use in severe asthma has recently been described (66,67). As magnesium inhibits catecholamine-induced arrhythmias, the possibility that magnesium may increase both the effectiveness and safety of β-agonists in the management of asthma is intriguing but has not yet been studied.

Genitourinary System

Magnesium is best known for its role in the management of gestational proteinuric hypertension in which it is used primarily as an anticonvulsant. It is also a powerful tocolytic and has been advocated for use in the management of premature labor. On the kidney, magnesium has a renal vasodilator effect, as well as a diuretic effect. No clinical use has been made of this potentially valuable action.

Musculoskeletal System

Magnesium exerts its major effect on muscles at the motor end plate, although it does have minor calcium antagonist properties on the muscle itself. This may have some benefit in the management of malignant hyperpyrexia (68), but the effect is small and probably not of great clinical significance.

Clinical Usage in Anesthesia

Although magnesium interacts with neuromuscular blocking drugs, prime attention should be placed on its cardiovascular effects with the actions of both a calcium antagonist with vasodilator and antiarrhythmic effects and an adrenergic antagonist with principally α-antagonistic actions. As a result of these dual actions, magnesium has a number of potential indications in anesthesia.

Obstetric Use

Magnesium is primarily used in obstetrics for prophylaxis and treatment of convulsions in the management of patients with gestational proteinuric hypertension. Magnesium inhibits the release of acetylcholine from the motor nerve terminal, and, to a lesser extent, decreases the sensitivity of the postjunctional membrane and reduces the excitability of the muscle fiber (69). The consequent enhancement of nondepolarizing neuromuscular blockers is of importance, and reduced dosages of these agents are recommended when $MgSO_4$ has been used, together with careful monitoring of neuromuscular transmission. Even the relatively short-acting relaxant vecuronium has been associated with significantly prolonged paralysis in the presence of high serum magnesium concentrations (38). Rapid rates of stimulation reverse a partial magnesium blockade, as opposed to the increasing blockade seen with *d*-tubocurarine. Perhaps *d*-tubocurarine inhibits the mobilization of acetylcholine, whereas magnesium does not (70). There is no good explanation as to why magnesium should enhance the effect of succinylcholine. Prolonged action of succinylcholine may be seen in the preeclamptic patient, but this is more likely to be due to the reduction in cholinesterase that accompanies the condition rather than to the use of magnesium (44). It must be emphasized that the presence of significant hypermagnesemia in the pregnant patient makes the use of defasciculating doses of nondepolarizing relaxants before induction of anesthesia not only unnecessary but potentially hazardous. Of more interest to the obstetric anesthetist is the ability of magnesium to alter the cardiovascular response to endotracheal intubation in patients with gestational proteinuric hypertension. We found that $MgSO_4$ (40 mg/kg) was superior to either lidocaine (1.5 mg/kg) or alfentanil (10 μg/kg) for the control of the hypertensive response to tracheal intubation in terms of the numbers of hypertensive episodes found. In addition, $MgSO_4$ and lidocaine both produced less fetal depression than did alfentanil. Alfentanil, however, produced better control of heart rate (71). A combination of 30 mg/kg of $MgSO_4$ with 7.5 μg/kg of alfentanil is superior to the larger dose of either agent alone, with no increase in side effects (72). For the very severe preeclamptic patient, a combination of $MgSO_4$ and alfentanil may be superior to magnesium alone.

In gravid ewes, magnesium reduces reflex sympathetic vasoconstriction in response to hypotension (73) and the hypertensive response to many vasoconstrictors (74). Although these actions may be beneficial in controlling pressor responses to events such as endotracheal intubation or straining during labor, they may also worsen hypotension in the presence of hemorrhage. In both studies, however, cardiac output was sustained, which is in line with earlier work (58). Magnesium will increase the likelihood of modest hypotension during epidural anesthesia in normotensive ewes, but this change is unlikely to be associated with increased risk to the fetus (75). Whether or not magnesium will increase the likelihood or severity of hypotension in patients with gestational proteinuric hypertension receiving epidural analgesia has not yet been studied. However, present evidence would tend to indicate that the sustained cardiac output and uterine blood flow will minimize the risks of hypotension to both mother and fetus.

Pheochromocytoma

The ability of magnesium to inhibit the release of catecholamines and to act as an antiadrenergic has recently been advanced as a rationale for the use of $MgSO_4$ infusions in the anesthetic management of patients undergoing resection of a pheochromocytoma (76). It would be expected that magnesium would be particularly effective during maneuvers that release catecholamines indirectly, such as induction of anesthesia, intubation of the trachea, and surgical stimulation, and this does, indeed, appear to be the case. Magnesium would likely be less effective during tumor handling when it would be less able to influence the release of catecholamines from the tumor. However, its peripheral antiadrenergic actions are still of substantial benefit. In addition to the reported series of 17 anesthetics (76), an additional 11 patients have been studied (James, unpublished data). In this series of 28 cases, $MgSO_4$ has been completely successful as a sole agent throughout 23 of the anesthetics even during periods of extensive tumor handling. A loading dose of 40–60 mg/kg followed by an infusion of 2 g/h was effective in controlling the response to endotracheal intubation and the early responses to operations in all patients. In 5 of the first 17 anesthetics, sodium nitroprusside infusions were needed during periods of tumor handling. Two of the patients in this series were pregnant and underwent cesarean section without simultaneous tumor removal. Magnesium was ineffective in one case, as therapeutic levels were never reached owing to gross preexisting deficits. In the other patient, magnesium alone provided excellent cardiovascular control during general anesthesia. As the safety of magnesium in pregnant patients is so well established, $MgSO_4$ has obvious appeal in the pregnant patient who also happens to have a pheochromocytoma (77).

Two cases have required postoperative adrenergic support (for 24 h and 6 h). Both patients had received relatively large doses of β-blockers on the morning of operation, and the duration of adrenaline infusion matched the duration of action of the agents used. It is possible that magnesium contributed to the need for postoperative adrenergic support, but there is evidence that magnesium does not inhibit the β_1-adrenergic actions of adrenaline nor does it diminish the effect of adrenaline on cardiac output (78,79). Nevertheless, caution must be advised when magnesium is used in a patient with a pheochromocytoma complicated by impaired myocardial contractility. It must also be borne in mind that significant down-regulation of adrenergic receptors may occur, and care should be exercised in patients in whom the level of symptomatology is much lower than would be anticipated for the catecholamine levels. Where hypotension after tumor excision occurs, calcium is an effective magnesium antagonist.

Vecuronium may be used in these cases, and because of its short duration of action, no problems of reversal of muscular relaxation have been experienced in association with concomitant large doses of $MgSO_4$. Before the availability of this muscle relaxant, prolonged paralysis owing to sustained serum magnesium levels was seen in one patient who had diminished renal function. In addition to magnesium, he had received alcuronium as the muscle relaxant and had needed sodium nitroprusside for additional arterial blood pressure control. The inhaled anesthetic in this case was enflurane. Prolonged paralysis was anticipated but caused no concern, as elective postoperative ventilation had been decided on preoperatively for other reasons (76).

Cardiovascular Anesthesia

In cardiac operations, magnesium has been a component of some cardioplegic solutions for many years and is thought to protect the ischemic myocardium (80) particularly during reperfusion (81). Magnesium is also of benefit in the early phase of ischemic contracture of the myocardium (82), and Manners and Nielson (83) recommended the return to the patient of magnesium-containing cardioplegic solution at the end of the bypass procedure because of its potential benefit to the recovering heart muscle. It will not interfere with the inotropic action of adrenaline (78), even in the postcardiopulmonary bypass patient (79). Although the value of various additives to cardioplegic solutions has been widely debated, magnesium depletion should be avoided scrupulously in the cardiac surgical patient, particularly in view of the adverse effects that magnesium deficiency may have in the patient with ischemic heart disease (84).

Magnesium is a valuable antiarrhythmic agent, particularly for those arrhythmias associated with digitalis, hypokalemia, alcoholism, and myocardial infarction, in addition to its inhibiting action on catecholamine-induced arrhythmias. It has also been recommended for intractable ventricular tachycardia and fibrillation, torsades de pointes, and multifocal atrial tachycardia (85). A bolus dose of 2 g of $MgSO_4$ administered over 5 min is generally recommended, followed by an infusion of the agent at a rate determined by the desired serum magnesium level but usually in the range of 1–2 g/h (85). No firm guidelines have been established for the most appropriate serum magnesium concentration in these circumstances, but a concentration of between 1.5 and 2 mmol/L has been reported as both safe and efficacious (86).

The vasodilator and antiarrhythmic properties of magnesium suggest that it may also be of use during aortic cross-clamping for major vascular operations, and we have occasionally used the agent successfully where other more conventional forms of treatment have been inadequate. An additional interesting possibility studied recently involves the role of magnesium as an *N*-methyl-D-aspartate antagonist. *N*-methyl-D-aspartate receptors mediate some of the pathological events after ischemia in neural tissue and magnesium may offer some protection to the spinal cord during the surgical repair of suprarenal aortic aneurysms (87).

Magnesium may also be considered for the control of the hypertensive response to endotracheal intubation. However, it must be borne in mind that magnesium will produce moderate tachycardia in most patients, so that this indication may be of limited value in patients with ischemic heart disease. In those patients in whom a mild increase in heart rate is not of great importance, $MgSO_4$ (40 mg/kg) may be a very useful method of controlling the response as it not only inhibits the increase in arterial blood pressure but also prevents catecholamine release (88) and exerts a significant antiarrhythmic effect.

Critical Care Medicine

The deleterious effects of magnesium deficiency are now well recognized in the intensive care unit, and most units now monitor magnesium levels to ensure that hypomagnesemia does not develop. Magnesium may, however, have value in this area as a therapeutic agent in several situations. In coronary care units, several studies have shown that the infusion of $MgSO_4$ can reduce the incidence and severity of cardiac arrhythmias associated with myocardial infarction (84,89); and in some studies, a reduced mortality has been demonstrated (90).

In the management of very severe tetanus, $MgSO_4$ infusions reduce cardiovascular instability (91) and inhibit the release of catecholamines (92). However, $MgSO_4$ is inadequate alone and must be used in conjunction with adequate sedation. In view of potential difficulties with prolonged $MgSO_4$ infusions, particularly alterations in calcium metabolism, $MgSO_4$ should be reserved for those patients in whom deep sedation proves inadequate to control cardiovascular instability. Combinations of magnesium with clonidine may also be useful (93).

There are now several reports of the bronchodilator effect of magnesium and of its successful use in the management of asthma (94–96). Its potential value in the treatment of this condition awaits further evaluation. The possibility that magnesium may decrease the incidence of adrenergically mediated arrhythmias without interfering with (and possibly enhancing) the bronchodilating action of the β-stimulants is intriguing.

Conclusions

Magnesium has several pharmacologic actions that may be of use in anesthesia. Its only major toxic effect is neuromuscular paralysis, and the route of elimination is renal, so that prolonged action may be anticipated where renal function is deficient. In particular, magnesium should be regarded first and foremost as a cardiovascular drug with calcium antagonistic and antiadrenergic properties that may be accompanied by minimal myocardial depression.

References

1. Zaloga G, Eisenach JC. Magnesium, anesthesia and hemodynamic control. Anesthesiology 1991;74:1–2.
2. Durlach J. Magnesium in clinical practice. London: John Libbey & Company, 1988:9–10.
3. Garfinkel L, Garfinkel D. Magnesium is an important coherent controller of glycolysis and the Krebs cycle. Magnesium 1985; 4:60–72.
4. Aikawa JK. Magnesium: its biological significance. Boca Raton, Fla.: CRC Press, 1981:21–9.
5. Wacker WEC. Magnesium and man. Cambridge, Mass.: Harvard University Press, 1980:11–51.
6. Hasselbach W, Fassold E, Migala A, Rauch B. Magnesium dependence of sarcoplasmic reticulum transport. Fed Proc 1981;40:2657–61.
7. Hodgkin AL, Keynes RD. Movement of labelled calcium in squid giant axons. J Physiol 1957;138:253–81.
8. Guillain F. Direct fluorescence measurements of Mg^{++} binding to sarcoplasmic reticulum ATPase. J Biol Chem 1982;257:7366–71.
9. Hubbard J, Jones S, Landall E. On the mechanism by which Ca^{2+} and Mg^{2+} affect the spontaneous release of transmitter from mammalian motor nerve terminals. J Physiol (London) 1968;194:355–80.
10. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. Am Heart J 1984;108:188–93.
11. Seelig M. Cardiovascular consequences of magnesium deficiency and loss: pathogenesis, prevalence and manifestations—magnesium and chloride loss in refractory potassium repletion. Am J Cardiol 1989;63:4G–21G.
12. Surawicz B. Is hypomagnesemia or magnesium deficiency arrhythmogenic? J Am Coll Cardiol 1989;14:1093–6.
13. Krasner B, Girdwood R, Smith H. The effect of slow releasing oral magnesium chloride on the QTc interval of the electrocardiogram during open heart surgery. Can Anaesth Soc J 1981; 28:329–33.
14. Krasner BS. Cardiac effects of magnesium with special reference to anaesthesia: a review. Can Anaesth Soc J 1979;26: 181–5.
15. Gambling DR, Birmingham CL, Jenkins LC. Magnesium and the anaesthetist. Can J Anaesth 1988;35:644–54.
16. Molloy DW, Dhingra S, Solven F, Wilson A, McCarthy DS. Hypomagnesemia and respiratory muscle power. Am Rev Respir Dis 1984;129:497–8.
17. Aikawa JK, Gordon GS, Rhoades EL. Magnesium metabolism in human beings: studies with Mg^{28}. J Appl Physiol 1968;15: 503–7.
18. Quamme GA, Dirks JH. The physiology of renal magnesium handling. Renal Physiol 1986;9:257–69.
19. Smith WO, Baxter DJ, Lindner A, Ginn HE. Effect of magnesium depletion on renal function in the rat. J Lab Clin Med 1962;59:211–9.
20. Meltzer SJ, Auer J. Physiological and pharmacological studies of magnesium salts. II. The toxicity of intravenous injections; in particular the effects upon the centers of the medulla. Am J Physiol 1906;15:387–405.
21. Peck CH, Meltzer SJ. Anesthesia in human beings by intravenous injection of magnesium sulphate. JAMA 1916;67:1131–3.
22. Aldrete JA. Magnesium physiology and pharmacology in anesthesia. Anesthesiol Rev 1987;14:33–9.
23. Somjen G, Hilmy M, Stephen CR. Failure to anesthetize human subjects by intravenous administration of magnesium sulfate. J Pharmacol 1966;154:652–9.
24. Feldberg W. Anesthesia and sleep-like conditions produced by injections into cerebral ventricles of cat. J Physiol (London) 1958;140:20P–1.
25. Chutkow JG. The neurophysiologic function of magnesium: an update. Magnesium-Bulletin 1981;1a:115–20.
26. Pritchard JA. The use of the magnesium ion in the management of eclamptic toxemias. Surg Gynecol Obstet 1955;100: 131–40.
27. Vandenplas O, Dive A, Dooms G, Mahieu P. Magnetic resonance evaluation of severe neurological disorders in eclampsia. Neuroradiology 1990;32:47–9.
28. Duncan R, Hadley D, Bone I, Symonds EN, Worthington BS, Rubin PC. Blindness in eclampsia: CT and MR imaging. J Neurol Neurosurg Psychiatry 1989;52:899–02.
29. Milliez J, Dahoun A, Boudraa M. Computed tomography of the brain in eclampsia. Obstet Gynecol 1990;75:975–80.
30. Trommer BL, Homer D, Mikhael MA. Cerebral vasospasm and eclampsia. Stroke 1988;19:326–9.
31. Sadeh M. Action of magnesium sulfate in the treatment of preeclampsia-eclampsia. Stroke 1989;20:1273–5.
32. Thompson SW, Moscicki JC, Difazio CA. The anesthetic contribution of magnesium sulphate and ritodrine hydrochloride in rats. Anesth Analg 1988;67:31–4.
33. Coutinho EM. Calcium, magnesium and local anesthesia. J Gen Physiol 1966;49:845–9.
34. Mordes JP, Wacker WEC. Excess magnesium. Pharmacol Rev 1978;29:273–300.
35. Krendal DA. Hypermagnesemia and neuromuscular transmission. Semin Neurol 1990;10:42–5.
36. Ghonheim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 1970;32:23–7.

37. Giesecke AH, Morris RE, Dalton MD, Stephen CR. Of magnesium, muscle relaxants, toxic parturients and cats. Anesth Analg 1968;47:689–93.
38. Sinatra RS, Philip BK, Naulty JS, Ostheimer GW. Prolonged neuromuscular blockade with vecuronium in a patient treated with magnesium sulfate. Anesth Analg 1985;64:1220–2.
39. James MFM, Schenk PA, Van der Veen BW. Priming of pancuronium with magnesium. Br J Anaesth 1991;66:247–9.
40. De Vore JS, Asrami R. Magnesium sulfate prevents succinylcholine induced fasciculations in toxemic parturients. Anesthesiology 1980;52:76–7.
41. Skaredoff MN, Roaf ER, Datta S. Hypermagnesaemia and anaesthetic management. Can Anaesth Soc J 1982;29:35–41.
42. James MFM, Cork RC, Dennett JE. Succinylcholine pretreatment with magnesium sulfate. Anesth Analg 1986;65:373–6.
43. Baraka A, Yazigi A. Neuromuscular interaction of magnesium with succinylcholine-vecuronium sequence in the eclamptic parturient. Anesthesiology 1987;67:806–8.
44. Kambam JR, Perry SM, Entman S, Smith BE. Effect of magnesium on plasma cholinesterase activity. Am J Obstet Gynecol 1988;159:309–11.
45. Aldrete JA, Zahler A, Aikawa JK. Prevention of succinylcholine induced hyperkalemia by magnesium sulphate. Can Anaesth Soc J 1970;17:477–84.
46. Hutter OF, Kostial K. Effect of magnesium and calcium ions on the release of acetylcholine. J Physiol 1954;124:234–41.
47. Somjen GG, Baskerville EN. Effect of excess magnesium on vagal inhibition and acetylcholine sensitivity of the mammalian heart in situ and in vitro. Nature 1968;217:679–80.
48. Altura BM, Altura BT. Magnesium and vascular tone and reactivity. Blood Vessels 1978;15:5–16.
49. Altura BM. Mg^{2+}-Ca^{2+} interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. Can J Physiol Pharmacol 1987;65:729–45.
50. Shine KI. Myocardial effects of magnesium. Am J Physiol 1979;237:H413–23.
51. Paddle BM, Haugaard N. Role of magnesium in effects of epinephrine on heart contraction and metabolism. Am J Physiol 1971;221:1178–84.
52. Bristow MR, Daniels RS, Kernoff RS, Harrison DC. Effect of D600, practolol, and alterations in magnesium on ionized calcium concentration-response relationships in the intact dog. Circ Res 1977;41:574–81.
53. Charbon GA. Unloading the heart by magnesium: the natural calcium competitor. Magnesium 1983;2:36–45.
54. Aldrete JA, Barnes DR, Aikawa JK. Does magnesium produce anesthesia? Anesth Analg 1968;47:428–33.
55. Critelli G, Ferro G, Peschle C, Perticone FR, Rengo FR, Condoreli M. Myocardial contractility after injection or prolonged infusion of magnesium sulfate. Acta Cardiol 1977;32:65–73.
56. Wallis DE, Gierke LW, Scanlon PJ, Wolfson PM, Kopp SJ. Sustained postischemic cardiodepression following magnesium-diltiazem cardioplegia (42355). Proc Soc Exp Biol Med 1986;182:375–85.
57. Dandavino A, Woods JR, Murayamak K, Brinkman C, Assali NS. Circulatory effects of magnesium sulfate in normotensive and renal hypertensive pregnant sheep. Am J Obstet Gynecol 1977;127:759–74.
58. James MFM, Cork RC, Dennett JE. Cardiovascular effects of magnesium sulfate in the baboon. Magnesium 1987;6:314–24.
59. Cotton DB, Gonik B, Karen F, Dornan RN. Cardiovascular alterations in severe pregnancy-induced hypertension: acute effects of intravenous magnesium sulfate. Am J Obstet Gynecol 1984;148:162–5.
60. Toda N, West TC. Interaction between Na, Ca, Mg, and vagal stimulation in the SA node of the rabbit. Am J Physiol 1967;212:424–30.
61. Iseri LT. Magnesium and cardiac arrhythmias. Magnesium 1986;5:111–26.
62. Mayer DB, Miletich DJ, Feld JM, Albrecht RF. The effects of magnesium salts on the duration of epinephrine-induced ventricular tachyarrhythmias in anesthetized rats. Anesthesiology 1989;71:923–8.
63. Solomon D, Bunegin I, Albin M. The effect of magnesium sulfate administration on cerebral and cardiac toxicity of bupivacaine in dogs. Anesthesiology 1990;73:341–6.
64. Haury VG. The broncho-dilator action of magnesium and its antagonistic action (dilator action) against pilocarpine, histamine, and barium chloride. J Pharmacol Exp Ther 1938;64:58–64.
65. Mathew R, Altura BM. Magnesium and the lungs. Magnesium 1988;7:173–87.
66. Okayama H, Aikawa T, Okayama M, Sasaki H, Mue S, Takishima T. Bronchodilating effect of intravenous magnesium sulfate in bronchial asthma. JAMA 1987;257:1076–8.
67. Noppen M, Vanmaele L, Impens N, Schandevyl W. Bronchodilating effect of intravenous magnesium sulfate in acute severe bronchial asthma. Chest 1990;97:373–6.
68. Flewellen EH, Nelson TE. In vivo and in vitro responses to magnesium sulphate in porcine malignant hyperthermia. Can Anaesth Soc J 1980;27:363–9.
69. Del Castillo J, Engbaek L. The nature of the neuromuscular block produced by magnesium. J Physiol 1954;124:370–84.
70. Foldes FF, Chaudry IA, Kinjo M, Nagashima H. Inhibition of mobilization of acetylcholine. Anesthesiology 1989;71:218–23.
71. Allen RW, James MFM, Uys PC. Attenuation of the pressor response to intubation in hypertensive proteinuric pregnant patients by lignocaine, alfentanil and magnesium. Br J Anaesth 1991;66:216–23.
72. Ashton WA, James MFM, Janicki PK, Uys PC. Attenuation of the pressor response to intubation in hypertensive proteinuric pregnant patients undergoing caesarean section by magnesium sulphate with and without alfentanil. Br J Anaesth 1991 (in press).
73. Liao J-C, Lijima T, Palahniuk RJ. Effect of magnesium sulfate on hemodynamic and reflex sympathetic vasoconstriction. Anesthesiology 1990;73:942A.
74. Sipes S, Chestnut D, Vincent R, Weiner C. Does magnesium sulfate alter the maternal cardiovascular response to vasopressor agents in gravid ewes? Anesthesiology 1990;73:A969.
75. Vincent RD, Chestnut DH, Sipes SL, Weiner CP, DeBruyn CS, Bleuer SA. Magnesium decreases maternal blood pressure but not uterine blood flow during epidural anesthesia in gravid ewes. Anesthesiology 1991;74:77–82.
76. James MFM. The role of magnesium sulphate in the anaesthetic management of phaeochromocytoma—a report of 17 anaesthetics. Br J Anaesth 1989;61:616–23.
77. James MFM, Huddle KRL, Owen AD, van der Veen BW. The use of magnesium sulphate in the anaesthetic management of phaeochromocytoma in pregnancy. Can J Anaesth 1988;35:178–82.
78. James MFM, Cork RC, Harlen GM, White JF. Interactions of adrenaline and magnesium on the cardiovascular system of the baboon. Magnesium 1988;7:37–43.
79. Prielipp RC, Zaloga GP, Butterworth JF, Robertie PG, Royster RL. Magnesium inhibits the α_1- but not the β_1-adrenergic actions of epinephrine in postoperative coronary artery bypass graft (CABG) patients. Anesthesiology 1990;73:A282.
80. Hearse DJ, Braimbridge MV, Jynge P. Protection of the ischemic myocardium: cardioplegia. New York: Raven, 1981.
81. Yano Y, Milam DF, Alexander JC. Terminal magnesium cardioplegia: protective effect in the isolated rat heart model using calcium accentuated ischemic damage. J Surg Res 1985;39:529–34.
82. Galloway PA, Lewer BMF, James MFM. Magnesium sulphate injection in the management of early ischaemic contracture of the myocardium. Anaesth Intensive Care 1986;14:321–3.
83. Manners JM, Nielson MS. Magnesium flux during open heart surgery. Anaesthesia 1981;36:157–66.

84. Rasmussen HS. Clinical intervention studies on magnesium in myocardial infarction. Magnesium 1989;8:316–25.
85. Iseri LT, Allen BJ, Brodsky MA. Magnesium therapy of cardiac arrhythmias in critical-care medicine. Magnesium 1989;8:299–306.
86. Iseri LT. Role of magnesium in cardiac tachyarrhythmias. Am J Cardiol 1990;65:47k–50k.
87. Amory DW, Jasaitis D, Wright C. Use of magnesium to protect against spinal cord ischemia. Anesthesiology 1990;73:A732.
88. James MFM, Beer RE, Esser JD. Intravenous magnesium sulfate inhibits catecholamine release associated with tracheal intubation. Anesth Analg 1989;68:772–6.
89. Bertschat F, Ising H, Gunther T, Sorgenfrei J, Wollitz M, Ibe K. Antiarrhythmic effects of magnesium infusions in patients with acute myocardial infarction. Magnesium-Bulletin 1989;11: 155–8.
90. Schechter M. Beneficial effect of magnesium in acute myocardial infarction. Magnesium-Bulletin 1990;12:1–5.
91. James MFM, Manson EDM. The use of magnesium sulphate infusions in the management of very severe tetanus. Intensive Care Med 1985;11:5–12.
92. Lipman J, James MFM, Erskine J, Plit ML, Eidelman J, Esser JD. Autonomic dysfunction in severe tetanus: magnesium sulfate as an adjunct to deep sedation. Crit Care Med 1987;15: 987–8.
93. Sutton DN, Tremlett MR, Woodcock TE, Nielsen MS. Management of autonomic dysfunction in severe tetanus: the use of magnesium sulphate and clonidine. Intensive Care Med 1990; 16:75–80.
94. Haury VG. Blood serum magnesium in bronchial asthma and its treatment by the administration of magnesium sulphate. J Lab Clin Med 1940;26:340–1.
95. Rolla G, Bucca C, Bugiani M, Arossa W, Spinaci S. Reduction of histamine-induced bronchoconstriction by magnesium in asthmatic subjects. Allergy 1987;42:186–8.
96. Carnes CA, Tyler LS. Magnesium in the treatment of bronchial constriction. Drug Intell Clin Pharm 1988;22:721–2.

Succinylcholine-Induced Prolonged Apnea in a 3-Week-Old Newborn: Treatment With Human Plasma Cholinesterase

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Prolonged respiratory depression can occur after administration of succinylcholine because of genetic plasma cholinesterase variants (1). Hanel et al. (2) found heterozygotes for the usual and atypical enzyme ($E_1^uE_1^a$) in 2.8% of all individuals investigated. A homozygous atypical cholinesterase phenotype ($E_1^aE_1^a$) is assumed to occur only with a frequency of 1 in about 2800 individuals (3). We describe treatment of succinylcholine-induced prolonged apnea in a 3-wk-old newborn with intravenous plasma cholinesterase.

Case Report

A 3-wk-old male newborn, body weight 3980 g, was admitted for pylorotomy. Laboratory data included a hematocrit of 41% and normal electrolytes. The family history was negative for anesthetic complications. The child received 0.1 mg of atropine 1 h before operation. Anesthesia was induced with 5 mg/kg IV thiopental. The patient received oxygen via a face mask, and 6 mg of succinylcholine was given intravenously followed by tracheal intubation. Anesthesia was maintained with 0.5% halothane in N_2O and O_2 (4:2 ratio). Intravenous fluids consisted of 5% dextrose in Ringer's solution. The operation was successfully completed 45 min after induction of anesthesia, and N_2O and halothane were discontinued. During the entire procedure, there were no abnormalities in continuously monitored electrocardiogram, rectal temperature, transcutaneous Po_2, and transcutaneous Pco_2 ($tcPo_2$, 90–130 mm Hg; $tcPco_2$, 29–34 mm Hg; TCM3, Radiometer, Denmark). Despite this uneventful intraoperative course, at the end of the procedure the neonate remained completely apneic. Controlled ventilation was continued with $tcPo_2$ ranging between 90 and 120 mm Hg and $tcPco_2$ between 40 and 50 mm Hg for 1 h. However, the neonate remained apneic and flaccid. The patient was tested for residual neuromuscular block without response even to supramaximal nerve stimulation. After 1 h of additional mechanical ventilation, repeated evaluation of neuromuscular function again showed no twitch or tetanus even at maximal voltage. Serum Cholinesterase P Behring (Behring AG, Marburg, Germany), equivalent to the plasma cholinesterase activity of 200 mL of adult human plasma, was then given. Serum Cholinesterase P Behring is a concentrate of the highly purified enzyme. The contents of one vial are equivalent in activity to 500 mL of fresh normal human plasma.

Recovery of neuromuscular function (train-of-four) and spontaneous breathing was observed within a few minutes after administration of the plasma cholinesterase, and the trachea could be extubated while $tcPo_2$ and $tcPco_2$ were monitored continuously. The patient did well postoperatively and showed no clinical signs of residual muscle weakness. Plasma cholinesterase was 4.41 kU/L on the first postoperative day (normal value: 3.5–8.5 kU/L). Three months after surgery blood samples were obtained from the patient and his family for estimation of plasma cholinesterase and dibucaine number. Determinations of the plasma cholinesterase activity (EC.3.1.1.8) and dibucaine number were performed by means of the butyrylthiocholine method (Greiner Diagnostica and Ciba-Geigy, Basel, Switzerland). Cholinesterase assay and estimation of dibucaine number indicated the patient to be homozygous for atypical cholinesterase, whereas his mother and his father were heterozygotes. The maternal grandmother and the paternal grandmother also were heterozygotes. The paternal grandfather was a normal homozygote; the maternal grandfather was dead (Table 1).

Discussion

Plasma cholinesterase concentrations in term neonates are about 50% that of adults, but by 2 wk of age cholinesterase concentrations are similar to those of adults (4). However, neonates and infants are more

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Table 1. Plasma Cholinesterase Concentration, Dibucaine Number, and Presumed Genotype of the Family

	Plasma cholinesterase (kU/L)	Dibucaine number (%)	Presumed genotype
Patient	2.29	11.3	$E_1{}^aE_1{}^a$
Mother	3.43	57.1	$E_1{}^aE_1{}^u$
Father	3.98	69.3	$E_1{}^aE_1{}^u$
Paternal grandmother	4.37	61.6	$E_1{}^aE_1{}^u$
Paternal grandfather	4.53	73.3	$E_1{}^uE_1{}^u$
Maternal grandfather		Not tested	
Maternal grandmother	4.60	67.2	$E_1{}^aE_1{}^u$
Normal values	3.5–8.5	~80	$E_1{}^uE_1{}^u$

resistant to a single dose or a continuous infusion of succinylcholine than older individuals (4,5).

Despite the lack of documentation in the literature, the incidence of succinylcholine-induced prolonged apnea in newborns must be considered to be the same as in adult individuals. Estimation of the dibucaine number (DN) is a standard technique for family surveys (1). According to the distribution of different plasma cholinesterase variants in the human population, Harris et al. (6) found a clear trimodal distribution for DN measurements indicating three distinct genotypes ($E_1{}^aE_1{}^a$, DN ~ 20; $E_1{}^uE_1{}^a$, DN ~ 60; $E_1{}^uE_1{}^u$, DN ~ 80). In contrast to patients homozygous for atypical plasma cholinesterase ($E_1{}^aE_1{}^a$) who are thought to be extremely sensitive to the administration of succinylcholine, Lehmann and Liddell (3) found the breakdown of succinylcholine in otherwise healthy heterozygous patients ($E_1{}^uE_1{}^a$) to be quite normal. Viby-Mogensen (7) also found only a slightly prolonged apnea after succinylcholine administration in heterozygous patients. In this study 13 of 28 patients (46%) with genotype $E_1{}^uE_1{}^a$ required more than 15 min for their twitch tension to return to control values and three of the patients (10.7%) required more than 20 min. This is seldom of any clinical significance. Our patient showed a profound neuromuscular blockade for nearly 3 h with no signs of spontaneous recovery before the administration of human plasma cholinesterase. Cholinesterase assay and estimation of DN confirmed that the patient was homozygous for atypical plasma cholinesterase, and the family survey revealed a clear inheritance from both the heterozygous parents. Horne et al. (8) reported the case of a 7-wk-old infant who had prolonged apnea secondary to abnormal cholinesterase of the following genotype: one "silent" gene and one atypical gene. The infant was only treated with mechanical ventilation for 5.5 h, but because of copious secretions the nasotracheal tube was left in place for 72 h.

The administration of human cholinesterase offers a new tool in the treatment of succinylcholine-induced prolonged neuromuscular blockade. Serum Cholinesterase P Behring is available for use only in Germany, Switzerland, and Austria. It is derived from donor plasma that is HBsAg-negative and anti-HIV-1, and then heat-treated in aqueous solution at 60°C for 10 h (pasteurization). Experiments in which a virus was added during processing have proven that this procedure inactivates DNA viruses (cytomegalovirus, herpes simplex) and RNA viruses (HIV-1, HIV-2, poliomyelitis) (9). Scholler et al. (10) found no unfavorable reactions after administration of human plasma cholinesterase to 15 patients with prolonged apnea after succinylcholine administration. There are no known contraindications for the use of human plasma cholinesterase.

Our case report illustrates that succinylcholine-induced prolonged neuromuscular blockade may also occur in the neonatal period. This complication can be successfully treated, even in earliest childhood, by intravenous administration of plasma cholinesterase with rapid recovery of neuromuscular function.

References

1. Whittaker M. Plasma cholinesterase variants and the anaesthetist. Anaesthesia 1980;35:174–97.
2. Hanel HK, Viby-Mogensen J, Schaffalitzky de Muckadell OB. Serum cholinesterase variants in the Danish population. Acta Anaesthesiol Scand 1978;22:505–7.
3. Lehmann H, Liddell J. Human cholinesterase (pseudocholinesterase): genetic variants and their recognition. Br J Anaesth 1969;41:235–44.
4. Cook DR, Fischer CG. Characteristics of succinylcholine on neuromuscular blockade in neonates. Anesth Analg 1978;57: 63–6.
5. Goudsouzian NG, Liu IMP. The neuromuscular response of infants to a continuous infusion of succinylcholine. Anesthesiology 1984;60:97–101.
6. Harris H, Whittaker M, Lehmann H, Silk E. The pseudocholinesterase variants. Esterase levels and dibucaine numbers in families selected through suxamethonium sensitive individuals. Acta Genet 1960;10:1–16.
7. Viby-Mogensen J. Succinylcholine neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. Anesthesiology 1981;55:231–5.
8. Horne JA, Watson TD, Giesecke AH, Prithvi Raj P, Ahlgren EW. Prolonged apnea in an infant following the use of succinylcholine. Anesthesiology 1973;39:545–7.
9. Hilfenhaus JW, Gregersen JP, Mehdi S, Volk R. Inactivation of HIV-1 and HIV-2 by various manufacturing procedures for human plasma proteins. Cancer Detect Prev 1990;14:369–75.
10. Scholler KL, Goedde HW, Benkmann HG. The use of serum cholinesterase in succinylcholine apnoea. Can Anaesth Soc J 1977;24:396–400.

Intravenous Regional Block Using Ketorolac: Preliminary Results in the Treatment of Reflex Sympathetic Dystrophy

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Intravenous regional blocks (IVRBs) with guanethidine have been widely used in the treatment of reflex sympathetic dystrophy (RSD) (1–3). Other drugs including ganglionic blockers, vasodilators, local anesthetics, and steroids have also been utilized (4). Steroids are especially useful in reducing the edema and joint tenderness associated with RSD (5). Ketorolac tromethamine (Toradol), a nonsteroidal antiinflammatory drug, is available for parenteral administration. We believed that ketorolac could be effective in treating RSD by IVRBs in a manner similar to steroids (5) but with relatively fewer side effects.

All ketorolac treatments were given using IVRB technique. After informed consent had been obtained, a cannula was introduced into a distal vein and cardiac monitoring was established. The affected extremity was elevated and exsanguinated using an Esmarch's bandage. After inflation of the tourniquet, the ketorolac solution was injected slowly over 4 min. Ketorolac, 60 mg in a total volume of 40 mL for upper extremities and 50 mL for lower extremities, was used. Normal saline or 0.5% lidocaine was used as the diluent (see Table 1). After 20 min, the cuff was deflated intermittently. Pain was assessed using a 0–10 pain scale (0 = no pain and 10 = worst pain imaginable).

Case Reports

The following case reports include seven patients diagnosed with RSD who were treated with ketorolac given by IVRB. Patients were diagnosed clinically based on the symptoms of allodynia and/or hyperpathia, burning pain, edema, color changes/hair growth changes, sweating changes, and temperature changes. In all cases, pain began after trauma to the extremity, with pain continuing after healing of the original injury. All patients had significant relief after appropriate sympathetic block.

A 33-year-old woman with a history of leg pain since fracturing the right tibia and fibula 7 yr earlier was referred to us for treatment of RSD. Her pain, which was constant, increased in the late afternoon and made ambulation difficult. Symptoms also included edema, color changes, and increased skin temperature in the affected extremity. The patient experienced complete relief of pain after successful lumbar sympathetic block. Upon return of pain, the patient was treated with an IVRB with ketorolac. Each time the pain returned to a significant level (>50%), a repeat block was given for a total of seven blocks. After this patient's first three blocks, pain decreased significantly (>50% reduction) for 3, 5, and 11 days, respectively. The patient has received seven blocks, and the duration of relief has increased with each subsequent block (see Table 1). The patient continues to be pain-free 36 days after the last injection.

Six other patients with clinical signs and symptoms of RSD of one extremity received one to four treatments with ketorolac per IVRB (see Table 1). After IVRB with ketorolac, all patients experienced significant relief of pain whether or not lidocaine was used. The duration of relief increased with each subsequent block in most cases. Burning during injection of ketorolac was the only side effect noted. Even though some burning occurred when the ketorolac was mixed with lidocaine, it was much milder than when saline was used.

Discussion

After initially obtaining very favorable results with IVRBs using ketorolac mixed with 0.5% lidocaine, blocks were also done with ketorolac mixed in normal saline so that relief could not be attributed to the effects of the local anesthetic. It appears that ketorolac given by IVRB did have a therapeutic effect on these

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Table 1. Summary of Blocks and Duration of Relief

Patient	Affected limb	Block		Pain before block[a]	Pain 30 min after IVRB[a]	Relief (days)[b]
		No.	Diluent			
1	Lower	1	Lidocaine	8	0	3
		2	Normal saline	5	1	5
		3	Lidocaine	7.5	0	11
		4	Normal saline	3	2	21
		5	Normal saline	8	0	30
		6	Normal saline	7	0.5	45
		7	Normal saline	10	1	36 (continues)
2	Upper	1	Normal saline	5	0	8
		2	Normal saline	1.5	0	7
		3	Lidocaine	2	0	3.5
		4	Lidocaine	2.5	0	16
3	Lower	1	Normal saline	3.5	0	<1
4	Upper	1	Normal saline	7	0	1
		2	Normal saline	7	4	10
5	Upper	1	Normal saline	6	0	<1
		2	Normal saline	6	2	7
		3	Normal saline	3	0	20
6	Lower	1	Lidocaine	10	0	60
7	Upper	1	Lidocaine	2.5	0	<1

IVRB, intravenous regional block.

[a] Pain was assessed on a 1–10 scale with 0 = no pain and 10 = worse pain imaginable.

[b] Mean duration = 15.1 ± 16.7 days.

seven patients with RSD. Duration of response tends to increase with subsequent blocks.

Ketorolac acts by inhibiting the cyclooxygenase enzyme and reducing prostaglandin synthesis. As prostaglandins sensitize pain receptors to both chemical and mechanical stimulation (6–8), reduction of prostaglandins should reduce this sensitivity. According to Roberts' (9) theory on the physiologic basis for causalgia and related pains, A-fiber mechanoreceptors may be activated by sympathetic efferent actions in the periphery. One possible mechanism by which this occurs is the presynaptic release of norepinephrine, which induces release of prostaglandins (10). Ketorolac may also produce benefits by interfering with the vasoconstriction produced by thromboxanes. Reduction in prostaglandin levels may lead to the inhibition of norepinephrine release and, in addition, may result in direct vasodilation. Previously reported relief with steroids (5) and with L-lysine (11) may rely on similar mechanisms. As the mechanism of action is distinct from that of sympathetic nerve blocks or IVRBs with guanethidine, it may be especially useful in combination with these other treatments or may be effective in a particular subset of patients. Double-blind studies are needed to establish ketorolac as an effective treatment. Studies should include a control group with systemically administered intramuscular ketorolac.

In conclusion, we report the use of ketorolac IVRB in patients who have RSD. It seems to produce prolonged pain relief in most patients with no serious side effects and may be a useful adjunct in the management of RSD.

References

1. Driessen J, Van Der Werken C, Nicolai JPA, Crul JF. Clinical effects of regional intravenous guanethidine (ismelin) in reflex sympathetic dystrophy. Acta Anaesthesiol Scand 1983;27:505–9.
2. Holland AJC, Davies KH, Wallace DH. Sympathetic blockade of isolated limbs by intravenous guanethidine. Can Anaesth Soc J 1977;24:597–602.
3. Bonelli S, Conoscente F, Movilia PG, Restelli L, Francucci B, Grossi E. Regional intravenous guanethidine vs. stellate ganglion block in reflex sympathetic dystrophies: a randomized trial. Pain 1983;16:297–307.
4. Lofstrom JB, Cousins MJ. Sympathetic neural blockade of upper and lower extremity. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. 2nd ed. Philadelphia: JB Lippincott, 1988:493–6.
5. Poplawski ZJ, Wiley AM, Murray JF. Post-traumatic dystrophy of the extremities—a clinical review and trial of treatment. J Bone Joint Surg 1983;65A:642–55.
6. Moncada S, Ferreira S, Vane J. Inhibition of prostaglandin biosynthesis as the mechanism of analgesia of aspirin-like drugs in the dog knee joint. Eur J Pharmacol 1975;31:250–60.
7. Chahl L, Iggo A. The effects of bradykinin and prostaglandin E_1 on rat cutaneous afferent nerve activity. Br J Pharmacol 1977;59:343–7.
8. Handwerker H. Influences of algogenic substances and pros-

taglandins on the discharges of unmyelinated cutaneous nerve fibers identified as nociceptors. In: Bonica JJ, Albe-Fessard D, eds. Advances in pain research and therapy. New York: Raven, 1976:41–5.

9. Roberts W. A hypothesis on the physiological basis for causalgia and related pains. Pain 1986;24:297–311.
10. Levine JD, Taiwo YO, Collins SD, Tam JK. Noradrenalin hyperalgesia is mediated through interaction with sympathetic postganglionic neurone terminals rather than activation of primary afferent nociceptors. Nature 1986;323:158–69.
11. Hannington-Kiff JG. Pharmacological target blocks in hand surgery and rehabilitation. J Hand Surg 1984;9B1:29–36.

Continuous Epidural Infusion of Bupivacaine and Fentanyl for Erythromelalgia in an Adolescent

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Erythromelalgia, or erythermalgia, is a rare syndrome characterized by burning pain, erythema, and elevated skin temperature of the hands, feet, or both when exposed to heat (1–4). It has been reported in 3 of 5000 patients referred to a pain clinic (5). Three recent reviews provide a complete description (5–7). The syndrome was first described in 1872 by Mitchell (8) and subdivided into primary or idiopathic and secondary forms in 1938 by Smith and Allen (9). Primary erythromelalgia occurs most frequently in middle-aged men, but up to one-third of the patients may be less than 30 yr of age (3,4). Secondary erythromelalgia has been described in association with many disorders (6) but is most commonly linked to the myeloproliferative diseases. In addition, secondary erythromelalgia occurs with equal frequency in both sexes and in an older population with a median age of 59 yr. No cases of secondary erythromelalgia have been described in children or adolescents (6). Exacerbations and remissions are common in both forms of the disorder. Attacks may last from minutes to days and are more common in the summer.

Intravascular platelet activation, aggregation, and arteriolar plugging may precipitate the syndrome (10,11). However, histopathologic studies of both primary and secondary erythromelalgia have had inconsistent findings. It is not clear if the two forms have the same pathologic origin (10–13). Pathologic studies from patients with secondary erythromelalgia associated with myeloproliferative diseases have shown intraarterial platelet thrombi (14). Biopsy findings in primary erythromelalgia have been variable, showing arteriolar plugging, thrombosis, fibrosis, and peripheral necrosis (12,13,15).

Several treatment modalities have met with inconsistent results (6). Relief of symptoms may be produced by elevation and cooling of the involved extremity. The syndrome may also be effectively treated with a single daily dose of aspirin (2–4,8,9); however, some patients do not respond to aspirin therapy (16,17). Only one case report has described the use of regional anesthesia to treat long-standing primary erythromelalgia (18). We report the use of a continuous epidural infusion for symptomatic relief followed by resolution of an acute exacerbation of erythromelalgia.

Case Report

A 15-yr-old boy was admitted for the evaluation of burning pain, redness, and swelling of the dorsal aspect of both feet. The patient had received an orthotopic heart transplant for treatment of an idiopathic cardiomyopathy 2 mo before admission. At the time of transplantation, incidental mediastinal adenopathy was noted and diagnosed as stage 1A Hodgkin's lymphoma. The patient received local radiation therapy for the lymphoma. When discharged home he was taking medications including FK-506 (an experimental immunosuppressant), acyclovir, Bactrim, and flurinef.

Since that time, the patient had experienced mild burning pain and erythema of the dorsum of his feet after showering with warm water. He experienced no discomfort in his hands. Symptomatic relief was achieved by placing his feet in cool water. Six days before admission he had suffered a mild, first-degree sunburn of his lower extremities that progressed to severe burning pain and erythema involving only the dorsal surface of his feet. The remaining areas of sunburn resolved within 2–3 days. Treatment with acetaminophen and propoxyphene was unsuccessful, and only continuous immersion of his feet in an ice-water bath achieved moderate relief. Discontinuation of the ice-water bath elicited an almost immediate increase in the severity of symptoms. The patient had difficulty sleeping and marked pedal edema developed over the next 6 days.

Physical examination revealed a young man in marked distress sitting with his feet immersed in ice

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water. The dorsal aspect of each foot was erythematous, exquisitely tender, and warm to touch. Edema extended midway up both lower legs, and the lateral aspects of both feet were mottled. Early signs of cold-water-immersion injury with cutaneous breakdown (trench foot) were present. Peripheral pulses and the neurologic examination were normal.

Laboratory tests revealed no abnormality on a complete blood cell count, a sequential multiple analysis of 20 chemical constituents, and a urine analysis. Antinuclear antibody titers, cryoglobulin screen, and antiviral antibodies were negative. A protein electrophoresis was normal.

The diagnosis of erythromelalgia was made on the basis of history and physical examination. There was concern for skin breakdown with secondary infection related to continued cold water immersion. Aspirin (650 mg) was administered without effect, and we were consulted for pain management. A lumbar epidural catheter was placed in the L3-4 interspace under sterile conditions. After a 3-mL test dose of 1.5% lidocaine with 1:200,000 epinephrine, 20 mL of 0.25% bupivacaine and 50 μg of fentanyl were injected into the epidural space. Over the next 0.5 h, the patient experienced complete symptomatic relief and a bilateral T10 sensory blockade. A continuous epidural infusion with 0.125% bupivacaine and 1 μg/mL of fentanyl at a rate of 12 mL/h was maintained over the next 60 h. During this time, the patient's feet were elevated and there was marked improvement in both the edema and the erythema. No complication resulted from epidural anesthesia. Aspirin therapy was continued (650 mg every 4 h), and no symptoms returned when the epidural infusion was discontinued. The patient has now been in remission for 1 yr.

Histopathologic results of a punch biopsy performed on the second day of the epidural infusion revealed diffuse necrosis of the superficial epidermis, plump basal epithelial cells with prominent nucleoli, and dermal vessels with scanty cuffs of lymphoid cells.

Discussion

We report a rare dermatologic condition that was resistant to conventional therapy but was successfully treated with a continuous epidural infusion of bupivacaine and fentanyl. Our patient exhibited the hallmark signs and symptoms of erythromelalgia, but his complex medical history and presentation made a definitive diagnosis difficult. His diagnosis of primary erythromelalgia was made by the consulting dermatologist because of the recurring nature of the disease and the trigger factors of each exacerbation, the appearance of the involved skin, and the resolution of symptoms in response to the described therapy. Secondary erythromelalgia has not been reported in an adolescent nor has it been described in association with an idiopathic cardiomyopathy or Hodgkin's lymphoma. In addition, none of the multiple medications that our patient was taking have been implicated as causal factors of this disorder. The histopathology of our patient was not diagnostic of erythromelalgia (10,11) nor did it rule out the presence of this disorder in which biopsy findings were unreliable and variable (12,13).

The use of a regional technique seemed appropriate even in our patient with his history of aspirin therapy. Although aspirin interferes with platelet function, aspirin therapy does not increase the risk of hemorrhagic complications associated with regional anesthesia (19). The technique of continuous epidural analgesia produced symptomatic relief, allowing the feet to be removed from the ice water and elevated. Thus, the epidural anesthesia was critical in preventing further cutaneous breakdown. Subsequent resolution may be attributable to several factors including delayed therapeutic benefit of aspirin, resolution of the sunburn, or the epidural anesthesia itself.

Epidural blockade to a T10 level in rhesus monkeys increases blood flow to the lower extremities (20). Increased blood flow to the extremity could decrease the effect of intraarteriolar platelet activation, aggregation, and plugging. Regional anesthesia, then, may be a viable treatment modality for acute exacerbation of erythromelalgia. Takeda et al. (18) demonstrated the use of bilateral lumbar sympathetic blockade and total spinal blockade to treat long-standing primary erythromelalgia.

The use of an epidural blockade resulted in improvement and resolution of erythromelalgia in this 15-yr-old boy. The relief of symptoms and prevention of further complications were evident. The underlying pathologic process may have been treated by the administration of epidural analgesics, but it is not possible to prove the efficacy of sympathetic blockade and peripheral vascular dilatation in patients with erythromelalgia from the events documented in this patient. However, we believe this technique may be useful in patients with this rare dermatologic disease.

References

1. Babb RR, Alorcan-Segovia D, Fairbairn JF II. Erythermalgia: review of 51 cases. Circulation 1964;29:136–41.
2. Bloom S. Erythromelalgia. N Y State Med J 1964;64:2470–1.
3. Mandell F, Folkman J, Matsumoto S. Erythromelalgia. Pediatrics 1977;59:45–8.
4. Thompson GH, Hahn G, Rang M. Erythromelalgia. Clin Orthop 1979;144:249–54.
5. Zoppi M, Zamponi A, Pagni E, Buoncristiano U. A way to understand erythromelalgia. J Auton Nerv Syst 1985;13:85–9.
6. Kurzrock R, Cohen PR. Erythromelalgia and myeloproliferative disorders. Arch Intern Med 1989;149:105–9.

7. Michiels JJ, van Joost T. Primary and secondary erythermalgia, a critical review. Neth J Med 1988;33:205–8.
8. Mitchell SW. Clinical lecture on certain painful affections of the feet. Philadelphia Med Times 1872;3:81–113.
9. Smith LA, Allen EV. Erythermalgia (erythromelalgia) of the extremities: a syndrome characterized by redness, heat, and pain. Am Heart J 1938;16:175–88.
10. Michiels JJ, Ten Kate FWJ, Vuzevski VD, Abels J. Histopathology of erythromelalgia in thrombocythaemia. Histopathology 1984;8:669–78.
11. Singh AK, Wetherley-Mein G. Microvascular occlusive lesions in primary thrombocythaemia. Br J Haematol 1977;36:553–64.
12. Priollet P, Bruneval P, Lazareth I, Vayssairat M, Mousset E, Barthelemy M. Erythromelalgia without arteriolar changes (letter). Ann Intern Med 1985;103:639.
13. Kvernebo K, Seem E. Erythromelalgia: pathophysiological and therapeutic aspects. A preliminary report. J Oslo City Hosp 1987;37:9–12.
14. Redding KG. Thrombocythemia as a cause of erythermalgia. Arch Dermatol 1977;113:468–71.
15. Uno H, Parker F. Autonomic innervation of the skin in primary erythermalgia. Arch Dermatol 1983;119:65–71.
16. Levine AM, Gustofson PR. Erythromelalgia: case report and literature review. Arch Phys Med Rehabil 1987;68:119–21.
17. Alarcon-Segovia D, Diaz-Jouanen E. Erythromelalgia in systemic lupus erythematosus. Am J Med Sci 1973;266:149–51.
18. Takeda S, Tomaru T, Higuchi M. A case of primary erythromelalgia (erythermalgia) treated with neural blockade. Masui 1989;38:388–93.
19. Horlocker TT, Wedel DJ, Offord KP. Does preoperative antiplatelet therapy increase the risk of hemorrhagic complications associated with regional anesthesia? Anesth Analg 1990;70:631–4.
20. Sivarajan M, Amory DW, Lindbloom LE. Systemic and regional blood flow during epidural anesthesia without epinephrine in the rhesus monkey. Anesthesiology 1965;45:300.

Acute and Long-Term Benefits of Iliac Crest Donor Site Perfusion With Local Anesthetics

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The operative site associated with most discomfort after orthopedic vertebral decompression and fusion with autogenous bone often is the donor site (i.e., the iliac crest). The purpose of this report is to relate our experience in treating this pain with postoperative bupivacaine infusion through a catheter whose tip is located at the iliac crest bone donor site. In addition, we sought to apply recent findings that effective perioperative analgesia may decrease the incidence and severity of long-term discomfort (1).

Methods

After institutional human investigational committee approval was obtained, 12 ASA physical status I or II patients scheduled for lumbar or cervical fusion with iliac crest bone grafting were recruited during a 6-mo period. Patients consented to intraoperative placement of an iliac crest catheter for local anesthetic perfusion and subsequent assessment of its efficacy. During the preoperative visit, patients were instructed on the use of visual analogue scoring (VAS) scale for pain (0 = no pain, 10 = worst pain imaginable).

After premedication with 5–10 mg of oral diazepam or 1–4 mg of intramuscular midazolam, anesthesia was induced with 3–5 mg/kg of thiopental and 1–2 μg/kg of fentanyl. After tracheal intubation, anesthesia was maintained with 66% nitrous oxide in oxygen and 1%–2% end-tidal isoflurane. Narcotics were administered as deemed indicated by the anesthesiologist assigned to provide medical care, and dosing was not prescribed by study design.

The vertebral fusions (nine lumbar, three cervical) were performed by the same orthopedic surgeons. In each patient, iliac crest bone was harvested as graft for 2–5 vertebral segments. Before surgical closure, a 20-gauge bullet-tip, three-orifice, radiopaque nylon catheter (Kendall Co., Boston, Mass.) was introduced percutaneously by the surgeon through a 17-gauge Weiss needle. The catheter was positioned to lie along the external surface of iliac crest bone donor site (deep to the periosteum) beside the surgical drain (Figure 1). After surgical closure and emergence from anesthesia, patients were transferred to the postanesthesia care unit.

When the patient first complained specifically of iliac crest bone discomfort, a VAS score for pain was recorded. Then, after negative aspiration of blood, 10 mL of 0.25% bupivacaine (25 mg) with 1:200,000 epinephrine was injected through the iliac crest catheter. This consisted of 3-mL as a test dose to confirm that the tip of the catheter was not intravascular, followed by an additional 7 mL. No parenteral analgesics were administered at this time. Fifteen minutes later, a VAS pain score again was obtained. Blood pressure (by automated sphygmomanometry) and heart rate (by electrocardiography) were monitored at 5-min intervals during and for 20 min after instillation of the local anesthetic. After transfer from the postanesthesia care unit to the hospital ward, all patients were allowed to obtain analgesia from intravenous morphine delivered by a patient-controlled analgesia pump. The patients also were instructed to request reinjection of local anesthetic into the iliac crest catheter if and when the donor site (specifically different from the vertebral surgical site) again became painful.

Each patient served as his/her own control with respect to the effect of the initial local anesthetic dose on the VAS pain score. In addition, postoperative patient-controlled analgesia narcotic requirements and long-term (6-mo) hip and back discomfort were compared with a matched historical control group of 12 patients in whom the same surgeons performed the same type of surgical procedures but did not use

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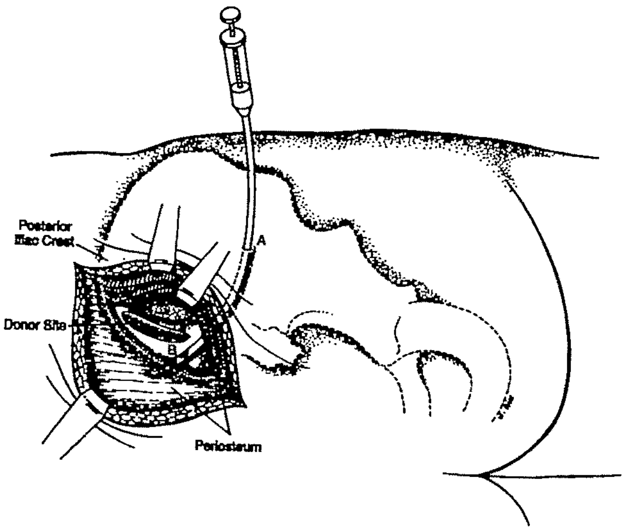

Figure 1. Catheter placement. A three-orifice catheter is placed through the skin overlying the iliac crest (*A*) to lie beside the surgical drain at the donor site (*B*). Before injection and for 10 min after injection, the surgical drain is clamped to prevent loss of injectate.

an iliac crest catheter for postoperative analgesia. Back pain and hip pain each was rated on the 0–10 VAS scale; "burning" and "tingling/numbness" at the iliac crest donor site each was rated on a 0–3 scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

Results

All patients could clearly differentiate pain at the donor site from pain at the site of vertebral fusion. Visual analogue scale scores for pain at the iliac crest bone donor site decreased in all patients in whom the donor site was perfused with bupivacaine, from a median of 7.0 (range 5–9) before injection to a median of 1.5 (range 0–4) after local anesthetic injection. The median duration of analgesia provided by the local anesthetic infiltration was 5.5 h (range 3–12 h). There were no instances of adverse local anesthetic reactions or wound complications.

Comparisons with the historical group of control patients are summarized in Table 1. In the immediate postoperative period, catheter-treated patients required significantly less morphine. Long-term follow-up was obtained in 11 patients from each group. At approximately 6 mo postoperatively, the median VAS scores for donor site pain were 4.0 and 0.5 for control and catheter-treated patients, respectively ($P < 0.05$). In contrast, median VAS scores for back pain (i.e., site of vertebral fusion) were 5.5 and 5.0, respectively (P = NS).

Table 1. Comparison of Study Group to a Matched Historical Control Group

	Control group	Treated group
PCA morphine usage (mg)		
24 h	90.8 ± 36.4	47.3 ± 25.0[a]
48 h	203.0 ± 48.4	118.4 ± 56.7[a]
Long-term symptoms		
Pain	6/11	2/11[a]
Mild	0	2
Moderate-severe	6	0
Dysesthesia	9/11	4/11[a]
Mild	1	4
Moderate-severe	8	0

PCA, patient-controlled analgesia.
[a] $P < 0.05$ for difference between control and treated groups.

Discussion

Donor site pain often constitutes the most intense pain experienced by patients after vertebral fusion surgery. Narcotic requirements of patients recovering from vertebral fusion (with bone graft) typically are twice those of patients recovering from laminectomy (without bone grafting) (2). Our data suggest that infusion of local anesthetic is an effective method of providing analgesia in this setting. Immediate effectiveness was evidenced by a marked decline in VAS pain scores. Long-term efficacy was evidenced by a significantly lower incidence of pain and dysesthesia 6 mo later. Consistent with the experience reported with local anesthetic perfusion of other sites (3–5), there were no untoward events. Effective relief was obtained with as little as 25 mg of bupivacaine, an important feature in view of the potentially rapid uptake of drug from the highly vascular injection site. Efficacy and safety may be even further assured by use of a continuous infusion; we presently are using a 0.25% solution at a rate of 5 mL/h.

The decrease in long-term sequelae in patients who received the local anesthetic infusion is consistent with decreased pain in patients who received local infiltration during herniorrhaphy (1). Several studies have noted that the analgesia provided by local anesthetics may outlast the expected duration of the anesthetics themselves (1,6). Recent evidence has suggested that prompt reduction of noxious afferent input may reduce the likelihood of prolonged or chronic pain (7), perhaps by reducing the spinal cord hyperexcitability and receptor field changes that otherwise may accompany deep tissue injury (8–11).

In conclusion, local anesthetic perfusion of an iliac crest donor site appears to be a very effective means of decreasing immediate and residual postoperative pain. It was associated with a prompt decrease in VAS pain scores, decreased 24- and 48-h narcotic requirements, and a lower incidence of severe residual symptoms.

References

1. Tverskoy M, Cozacov C, Ayache M, Bradley EL Jr, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. Anesth Analg 1990;70:29–35.
2. Preble L, Paige D, Sinatra R, O'Connor TZ, Sevarino FB. Varying narcotic requirements among orthopedic patients. Anesthesiology 1990;73:A813.
3. Patel JM, Lanzafame RJ, Williams JS, Mullen BV, Hinshaw JR. The effect of incisional infiltration of bupivacaine hydrochloride upon pulmonary functions, atelectasis and narcotic need following elective cholecystectomy. Surg Gynecol Obstet 1983; 157:338–40.
4. Dinley J, Dickson RA. The control of pain after Keller's operation by the instillation of local anaesthetic before closure. J Bone Joint Surg 1976;58B:356–8.
5. Gibbs P, Purushotham A, Auld C, Cuschieri RJ. Continuous wound perfusion with bupivacaine for postoperative wound pain. Br J Surg 1988;75:923–4.
6. Young DV. Comparison of local, spinal, and general anesthesia for inguinal herniorrhaphy. Am J Surg 1987;153:560–3.
7. Wall PD. The prevention of postoperative pain. Pain 1988;33: 289–90.
8. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686–8.
9. Sugimoto T, Takemura M, Sakai A, Ishimaru M. Rapid transneuronal destruction following peripheral nerve transection in the medullary dorsal horn is enhanced by strychnine, picrotoxin and bicuculline. Pain 1987;30:385–93.
10. Cook AJ, Woolf CJ, Wall PD, McMahon SB. Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. Nature 1987;325:151–3.
11. Wall PD, Woolf CJ. The brief and the prolonged facilitatory effects of unmyelinated afferent input on the rat spinal cord are independently influenced by peripheral nerve section. Neuroscience 1986;17:1199–205.

Massive Intraoperative Pulmonary Embolism: Diagnosis With Transesophageal Two-Dimensional Echocardiography

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Intraoperative pulmonary thromboembolism (PTE) is rare. Diagnosis of PTE is often difficult in the operating room (OR) owing to lack of specificity of initial symptoms and difficulty in performing a diagnostic procedure, such as pulmonary scintigraphy or angiography. Thus, diagnosis is often suspected later when the anesthesiologist is faced with cardiac arrest (1–5). This case illustrates utility of transesophageal echocardiography in the early diagnosis and management of an intraoperative massive PTE.

Case Report

A 38-yr-old man was admitted for treatment of a large chondrosarcoma, initially located at the level of the fifth lumbar vertebra, which had developed anteriorly, shifting abdominal organs to the left. Diagnosis was confirmed by surgical biopsy under general anesthesia without incident. Ten days later, the patient was scheduled for resection. Preoperative assessment included phlebocavography, which revealed a shift of the vena cava to the left without thrombosis 5 days before surgery. This patient had no prior cardiopulmonary disease, nor was he taking medication.

Flunitrazepam (1 mg) was administered orally 1 h before surgery. Before anesthesia induction, peripheral intravenous and radial artery catheters were inserted. At this time, oxygen arterial saturation (Spo_2) measured with a pulse oximeter was 90% while the patient was drowsy and was breathing room air; Spo_2 increased to 100% during preoxygenation. Anesthesia was induced with fentanyl (2 μg/kg) and thiopentone (4 mg/kg), and muscular relaxation was achieved with vecuronium (0.1 mg/kg). The trachea was intubated and anesthesia was maintained with 60% nitrous oxide in oxygen, fentanyl, and isoflurane. Monitoring included arterial blood pressure and esophageal temperature measurements, electrocardiography, pulse oximetry, and mass spectrometry enabling expired gas analysis.

Twenty-five minutes after induction, arterial blood pressure abruptly decreased from 100/60 to 60/40 mm Hg. At this time, Spo_2 also abruptly decreased to 85%, so that inspired oxygen concentration was increased to 100%. Arterial blood pressure increased to 90/60 mm Hg after ephedrine administration (6 mg) and remained stable thereafter without any further hemodynamic support. Blood gas analysis showed arterial hypoxemia at 78 mm Hg with severe hypercapnia at 61 mm Hg and a pH of 7.12. At the same time a low end-tidal carbon dioxide level of 24 mm Hg was noted. Breath sounds remained clear and symmetrical, with unchanged airway pressure between 24 and 30 cm H_2O. Fiberoptic bronchoscopy confirmed the correct position of the endotracheal tube. There were no signs of aspiration. A chest roentgenogram performed in the OR was normal. Electrocardiography showed only a sinus tachycardia (110 beats/min). Massive PTE was suspected and transesophageal echocardiography was performed in the OR.

Transesophageal echocardiography showed acute dilation of the right atrium and right ventricle in the four-chamber view (Figure 1), with enlargement of the pulmonary artery (Figure 2). Spontaneous contrast was observed in the right cavities; this echocardiographic sign is related to decreased blood flow. A shift in both atrial and ventricular septa was apparent (Figure 1). During this examination, actual migration of a thrombus from the right atrium (Figure 1A) to the right ventricle (Figure 1B) was observed. Contrast echocardiography with microbubbles (intravenous injection of 10 mL of colloid solution mixed with 0.2 mL of air) did not show any patent foramen ovale. Cardiac index was computed at 2.45 $L \cdot min^{-1} \cdot m^{-2}$, using the Teichholz method (6). Considering these echocardiographic findings in favor of a massive PTE, we decided to stop surgery and to perform an inter-

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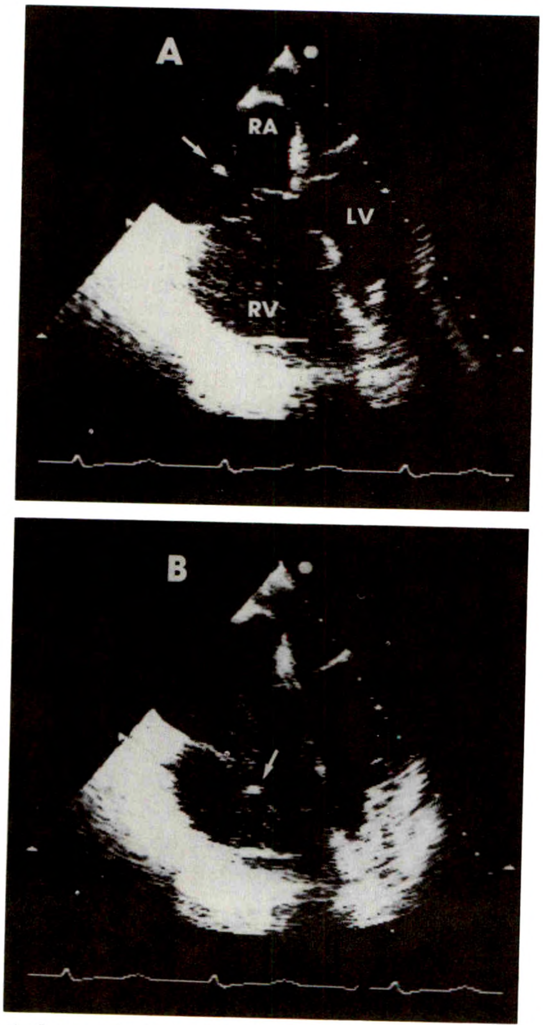

Figure 1. Long-axis four-chamber view of the heart. The *arrows* show the thromboembolus, which migrates from the right atrium (RA) to the right ventricle (RV). Spontaneous contrast is observed in the right ventricle. LV, left ventricle.

ruption of the inferior vena cava using a clip to prevent a fatal recurrent embolism. Heparinization was immediately started. Immediately after surgery, a pulmonary angiogram confirmed a massive PTE with an obstruction estimated at 75%. Clinical evolution was then uneventful and a pulmonary angiogram 10 days later was normal. The patient was discharged from the intensive care unit 2 wk later.

Discussion

Massive PTE is associated with a sudden reduction of pulmonary arterial bed and an increase in right ventricular afterload and produces acute right ventricular failure and systemic hypotension.

Hemodynamic findings in patients without prior cardiopulmonary disease, as in our patient, are well correlated with angiographic severity index of embolic obstruction (7,8). Diagnosis of intraoperative PTE has been made in most cases retrospectively by lung perfusion scan (2,9), pulmonary angiogram (10,11), pulmonary embolectomy (3), or even postmortem examination (4,5). This emphasizes the difficulty in diagnosing PTE in the OR. Unfortunately, diagnosis is often suspected only after a collapse has occurred (1–5,10,12). At this late stage, critical hemodynamic conditions do not enable appropriate investigations such as pulmonary perfusion scan or angiogram, and often lead to rapid cardiac arrest (1–5). The other main sign found in many case reports of intraoperative PTE is hypoxemia (2,3,9–13). Hypoxemia is frequent but not constant in PTE (13,14) and has been shown to be proportional to the extent of pulmonary obstruction (7). The Sp_{O_2} of 90% before anesthesia induction might have been related to flunitrazepam administration. We cannot rule out the hypothesis of previous nonmassive PTE leading to hypoxemia but not hemodynamic disturbances. A persistent Sp_{O_2} of 85% (with an F_{IO_2} of 40%) was noted, leading us to perform arterial blood gas analysis. We observed an end-tidal carbon dioxide level of between 23 and 25 mm Hg, with stable hemodynamic status, and a large increase of the arterial to end-tidal carbon dioxide tension gradient ($P(a\text{-}ET)_{CO_2}$: 37 mm Hg). In fact, PTE leads to a large alveolar dead space, which increases $P(a\text{-}ET)_{CO_2}$. Analysis of alveolar dead space has been proposed as a simple and reliable means of diagnosing PTE in patients with normal lung function and in most patients with pulmonary disease (15), so the major increase of $P(a\text{-}ET)_{CO_2}$ seems to be of great diagnostic value and emphasizes the importance of blood gas analysis and end-tidal carbon dioxide level monitoring. Hypocapnia is usually observed during

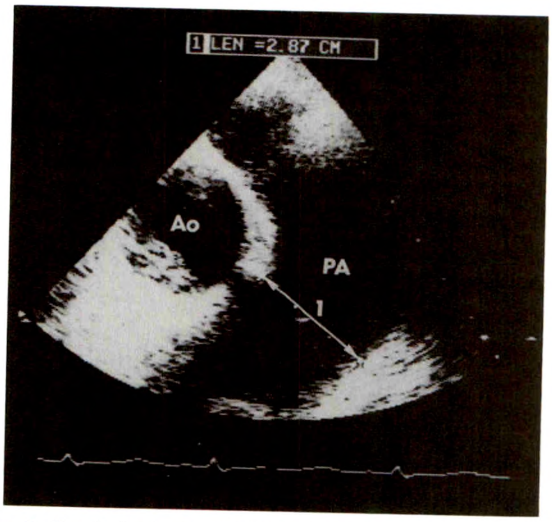

Figure 2. Basal short axis view showing the enlargement of the pulmonary artery (PA). Ao, aorta.

PTE. In our patient, hypercapnia was related to mechanical ventilation impeding spontaneous hyperventilation usually occurring in PTE. Indeed hypercapnia has also been noted in previous case reports of PTE in the OR (3,11,12).

A Swan-Ganz catheter could have provided some information concerning the hemodynamic status (12). It is not a specific procedure for diagnosis of PTE (16) even though some changes may occur in massive PTE. Bedside angiography using a Swan-Ganz catheter has been advocated for the diagnosis of PTE in the OR (10,11) but, because the catheter is flow-directed, a false-negative result with a normal angiogram of one patent pulmonary vessel is likely to occur.

Echocardiography was an important technique in the diagnosis of massive PTE in our patient. A close correlation has been demonstrated between size of the right pulmonary artery and mean pulmonary artery pressure in patients with PTE and without prior cardiopulmonary disease (8). Changes in the right to left ventricular end-diastolic area ratio have also been reported to correlate with severity of pulmonary obstruction (8). Other indirect signs of PTE, such as an abnormal interventricular septum contracting pattern can be observed in massive PTE (8,17). This phenomenon is maximum during the acute phase of PTE and emphasizes the importance of ventricular interdependence, which is associated with pulmonary artery obstruction decreasing left ventricular preload and producing circulatory failure.

These echocardiographic changes are indirect signs of PTE and result from acute pulmonary hypertension, which is significant when pulmonary artery obstruction exceeds 30% (7). Direct visualization of thromboembolus either in right-sided cavities by transthoracic echocardiography (18) or in the pulmonary artery by transesophageal echocardiography have been previously reported (19). Intraoperative thromboembolus migration under echocardiographic vision has not been described before. Visualization of thromboembolism in the pulmonary artery and thromboembolus migration are the only two direct echocardiographic signs of PTE. Transesophageal echocardiography may provide other information: (a) detection of constant or intermittent intracardiac shunting through a patent foramen ovale, especially if severe hypoxemia or paradoxical embolism occurs; (b) evaluation of left ventricular function and the noninvasive determination of cardiac output; and (c) supervision of the hemodynamic status.

In conclusion, this case suggests the utility of transesophageal echocardiography in diagnosing intraoperative PTE using a noninvasive and rapid procedure that enables management of the patient, including interruption of the vena cava, without any delay before a fatal recurrent embolism has occurred.

References

1. Divekar VM, Kamdar BM, Pansare SN. Pulmonary embolism during anaesthesia: case report. Can Anaesth Soc J 1981;28:277–9.
2. Goodman NW, Falkner MJ. Massive intraoperative pulmonary embolism in a child. Br J Anaesth 1987;59:1059–62.
3. Hecker BR, Lynch C. Intraoperative diagnosis and treatment of massive pulmonary embolism complicating surgery on the abdominal aorta. Br J Anaesth 1983;55:689–91.
4. Navalgund AA, Kang Y, Sarner JB, Jahr JS, Gieraerts R. Massive pulmonary thromboembolism during liver transplantation. Anesth Analg 1988;67:400–2.
5. Pollard BJ, Pharm B, Lovelock HA, Jones RM. Fatal pulmonary embolism secondary to limb exsanguination. Anesthesiology 1983;58:373–4.
6. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determination: echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976;37:7–11.
7. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 1971;28:288–94.
8. Kasper W, Meinertz T, Kerting F, Lollgen H, Limbourg P, Just H. Echocardiography in assessing acute pulmonary hypertension due to pulmonary embolism. Am J Cardiol 1980;45:567–72.
9. Enright AC, Quartey GRC, McQueen JD. Pulmonary embolism during operation. Can Anaesth Soc J 1980;27:65–7.
10. Berry AJ. Pulmonary embolism during spinal anesthesia: angiographic diagnosis via a flow-directed pulmonary artery catheter. Anesthesiology 1982;57:57–9.
11. Oxorn DC, Skurdal D, Belzerg H, Rosenbaum RC. Pneumothorax and pulmonary embolism complicating post-traumatic hip surgery. Can J Anaesth 1987;34:174–7.
12. Mangano DT. Immediate hemodynamic and pulmonary changes following pulmonary thromboembolism. Anesthesiology 1980;52:173–5.
13. Cvitanic O, Marino PL. Improved use of arterial blood gas analysis in suspected pulmonary embolism. Chest 1989;95:48–51.
14. Jardin F, Gurdjian F, Desfonds P, Fouilladieu JL, Margairaz A. Hemodynamic factors influencing arterial hypoxemia in massive pulmonary embolism with circulatory failure. Circulation 1979;59:909–12.
15. Eriksson L, Wollmer P, Olsson KG, et al. Diagnosis of pulmonary embolism based upon alveolar dead space analysis. Chest 1989;96:357–62.
16. Dehring DJ, Arens JF. Pulmonary thromboembolism: disease recognition and patient management. Anesthesiology 1990;73:146–64.
17. Jardin F, Dubourg O, Gueret P, Delorme G, Bourdarias JP. Quantitative two-dimensional echocardiography in massive pulmonary embolism: emphasis on ventricular interdependence and leftward septal displacement. J Am Coll Cardiol 1987;10:1201–6.
18. Starkey IR, De Bono DP. Echocardiographic identification of right-sided cardiac intracavitary thromboembolus in massive pulmonary embolism. Circulation 1982;66:1322–5.
19. Nixdorff U, Erbel R, Drexler M, Meyer J. Detection of thromboembolus of the right pulmonary artery by transesophageal two-dimensional echocardiography. Am J Cardiol 1988;61:488–9.

Venous Air Embolism During Radical Retropubic Prostatectomy

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A radical retropubic prostatectomy is often performed with the patient in a head-down tilt (Trendelenburg) position and, therefore, a gravitational gradient can exist between the right side of the heart and the prostatic fossa. In the case of an open venous sinus or vein, venous air embolism (VAE) can occur (1–4). We describe a patient undergoing radical retropubic prostatectomy who was exposed to intermittent episodes of VAE.

Case Report

A 72-yr-old, 70-kg man with prostatic cancer was scheduled for pelvic lymph node dissection and radical retropubic prostatectomy. The patient had been taking α-methyl dopa/hydrochlothiazide for hypertension. He had a 15 pack per year smoking history but otherwise was healthy. Physical examination was unremarkable except for a grade II/VI systolic ejection murmur at the left sternal border without radiation. Midazolam (1 mg), ranitidine (150 mg), and metoclopramide (10 mg) were given orally with his hypertensive medication on the morning of surgery.

In the operating room while the patient was under mild intravenous sedation (50 μg of fentanyl and 1 mg of midazolam), a left radial arterial line and a right antecubital vein, long-arm, multiorificed central line were inserted, the latter of which was at the junction of the right atrium and superior vena cava as confirmed by a radiograph. Standard monitors were used including continuous end-tidal CO_2 readings and precordial Doppler. Anesthesia was induced with intravenous thiopental and fentanyl with endotracheal intubation facilitated by intravenous administration of succinylcholine. The patient was positioned and the precordial Doppler probe was placed just left of the lower sternum. Positioning involved a 15° head-down tilt and the gradient was calculated at 10.0 cm. Anesthesia was maintained with N_2O, isoflurane, fentanyl, and pancuronium. Ventilation was controlled. The patient had transient hypertension at the start of surgery but remained stable throughout the node biopsies which took approximately 1 h. The findings from frozen sections of the nodes were negative and prostatectomy was undertaken. Air was detected by the Doppler on three occasions without hemodynamic consequences, and no air was aspirated. Nitrous oxide was then discontinued for the remainder of the surgery and 100% oxygen was given. Thirty minutes after starting the prostatectomy, there was significant bleeding and packed red blood cells were transfused. Thirty minutes later, air was detected by the Doppler. The arterial blood pressure decreased from 128/60 to 92/38 mm Hg, end-tidal CO_2 decreased from 4.3% to 3.9%, and nitrogen was detected by mass spectrography. Aspiration from the central line catheter yielded 20 mL of frothy air bubbles. Within 5 min, baseline hemodynamics returned. The Doppler detected air intermittently throughout the course of surgery but no hemodynamic sequelae occurred, and no air could be aspirated from the catheter. The estimated blood loss was 7.8 L and was replaced with packed red blood cells, hetastarch, salt-poor albumin, and lactated Ringer's solution. The operative procedure lasted approximately 6 h.

Discussion

The rich vascularity of the prostate is often not appreciated (5). The prostate is a chestnut-shaped, muscular, glandular structure that lies behind the pubic bone, between the bladder neck and the urogenital diaphragm (Figure 1). Its normal weight is about 20 g but benign hypertrophy can increase its weight up to 100 g. It is firmly invested by fascia. Posteriorly, Denonvillers fascia separates the prostate

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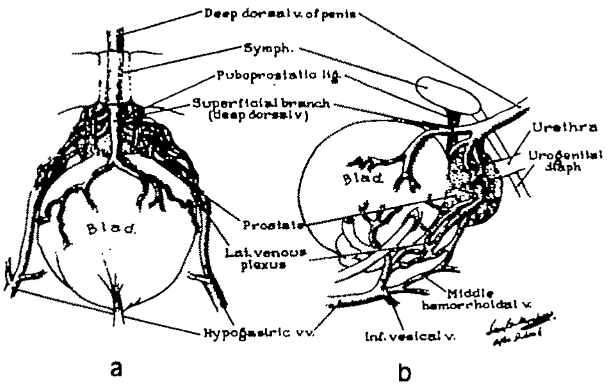

Figure 1. Frontal (**a**) and lateral (**b**) views of Santorini's plexus and the deep dorsal vein of the penis. This illustrates the heavy vascularization of the periprostatic structures. (From WG Reiner, PC Walsh. An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. J Urol 1979;121:198–200. © by Williams & Wilkins, 1979.)

from the rectum. Laterally, a reflection of the endopelvic fascia forms a sheath that covers the prostate. The venous drainage from the prostate is through numerous small veins that join a rich venous plexus, the plexus of Santorini, which is between the prostate and its covering of endopelvic fascia. In addition to veins from the prostate, the plexus of Santorini also receives veins from the penis (deep dorsal vein) and the bladder and seminal vesicles (6). The plexus has three divisions: one anterior to the prostate and one on each side. The lateral divisions each coalesce at the base of the bladder to form inferior vesical veins that drain into the internal iliac veins. There is communication between the veins of Santorini's plexus and the pubic, pudendal, deep epigastric, obturator, and hemorrhoidal veins. Santorini's plexus also communicates with the presacral prevertebral venous plexus (Batson's plexus).

This patient first underwent a pelvic lymph node dissection followed by a radical retropubic prostatectomy once the lymph nodes were found to be noncancerous. The patient had a clinical stage B adenocarcinoma of the prostate. After the lymph node tissue in both iliac fossae were removed following an infraumbilical midline incision, the prostate was exposed. The puboprostatic ligaments were incised at the pubis to avoid traumatizing the significant dorsal venous plexus surrounding the prostate. The lateral endopelvic fascia was incised to expose the lateral walls of the prostate. The dorsal venous complex was then isolated and doubly ligated with silk ties and chromic sutures were placed distal to these ties on the venous complex to avoid back bleeding. Although the venous complex was incised between the ties, significant bleeding was noted from residual veins surrounding the prostate. Once the bleeding was under control, the urethra distal to the prostate was incised and the prostatic branches of the lateral vascular pedicles were ligated to free the prostate distally. The bladder neck was then opened anteriorly and the prostate was excised en bloc with the seminal vesicles. Venous bleeding surrounding the bladder neck and on the pelvic floor was controlled with multiple ligation sutures. The bladder neck was then sutured to the distal stump over a Silastic Foley catheter. Drains were placed lateral to the anastomosis and the wound was closed.

This case report demonstrates the problems associated with the combination of a gravitational gradient, a heavily vascularized surgical territory, blood loss, and the subsequent development of episodic venous air embolism. Our decision to monitor this case for potential VAE was based on a previous retropubic radical prostatectomy carried out in extreme Trendelenburg position, and shoulder braces were used to prevent downward slippage. Marked hypotension (lasting 15 min), tachycardia, and bouts of supraventricular tachycardia occurred about 15 min after a period of pronounced bleeding and adequate blood volume replacement. A "roaring" murmur lasting for about 5–10 s was also heard through the esophageal stethoscope. These responses suggested that VAE had occurred in this patient.

Of interest in this case were the multiple episodes of Doppler-detected VAE without the ability to aspirate air through the central line. Several authors have noted that the precordial Doppler can detect as little as 100 μL of air passing the sensor (7–9). The excellent reliability of the precordial Doppler to detect air bubbles was also noted by Fong et al. (10) who monitored patients undergoing cesarean section in the horizontal position using two-dimensional echocardiography and a precordial Doppler. They found a perfect correlation between the precordial Doppler and echocardiography (κ value = 1) in the 49 patients in the study with an incidence of VAE of 29% (14 of 49). Equally important, the emboli detected by the precordial Doppler were air bubbles and not signals characteristic of amniotic fluid or thromboemboli. Gibby (11) has noted that the sensitivity of the precordial Doppler for air bubble detection lies in the same range as the transesophageal echocardiograph. Although the precordial Doppler has excellent sensitivity and reliability, there is a time lag between the moment of Doppler activation with an auditory signal and the manual aspiration of the central line. Thus, small volumes of air may pass the tip of the central line before aspiration occurs and the bubbles then enter the right atrium.

The position used in this case is similar to that noted in Figure 2, with the table broken and a

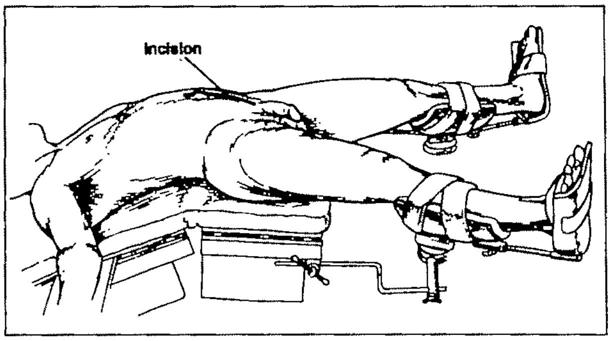

Figure 2. Position used for radical retropubic prostatectomy. There is a break in the table and the trunk is placed in a dependent position. (From Brendler CB. Potency-preserving radical cystoprostatectomy. Contemp Urol 1990; November: 47–55. Published with permission of the artist, John Foerster).

significant gravitational gradient established between the right side of the heart and the region of the prostate. In the urologic literature, Hinman (12) has recommended that a 20° Trendelenburg position be used for radical retropubic prostatectomy. Although we have not been able to ascertain any other cases of VAE during radical retropubic prostatectomy in the medical literature, there have been reports in other types of urologic procedures. Fatal air embolism during transurethral resection of the prostate has been described by Salo in 1971 and by Hofsess in 1984 (13,14). Recently, Vacanti and Lodhia (15) noted a third case of fatal air embolism occurring while a transurethral resection of the prostate was being performed. Pyron and Segal (16) described two cases of VAE during retrograde pyelography and Miller et al. (17) described VAE moving into the hepatic veins during percutaneous nephrolithotomy.

Because of the rich vascularity of the prostate, we believe a multiorificed central line for air aspiration and a precordial Doppler should be used during a radical retropubic prostatectomy if the possibility exists that positioning would involve the development of a gravitational gradient.

References

1. Amussat JZ. Recherches sur l'introduction accidentelle de l'air dans les veins. Paris: Germer Bailliere, 1839:255.
2. Michenfelder JD, Terry HR Jr, Daw EF, Miller RH. Air embolism during neurosurgery: a new method of treatment. Anesth Analg 1966;45:390–5.
3. Maroon JC, Goodman JM, Horner TC. Detection of minute venous air emboli with ultrasound. Surg Gynecol Obstet 1968;127:1236–8.
4. Albin MS, Babinski M, Maroon JC, Jannetta PS. Anesthetic management of posterior fossa surgery in the sitting position. Acta Anesthesiol Scand 1976;20:117–28.
5. Zimskind PD, Kelsey DM, Koppel MM. The anatomy and surgical approach to the lower urinary tract and genitalia. In: Kendall AR, Karafin L, eds. Urology. Philadelphia: Harper & Row, 1984:13–5.
6. Reiner WG, Walsh PC. An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. J Urol 1979;121:198–200.
7. Chang J, Albin MD, Bunegin L, Hunt T. Analysis and comparison of venous air embolism detection methods. Neurosurgery 1980;7:135–41.
8. Gildenberg PL, O'Brien RP, Britt WJ, Frost EA. The efficacy of Doppler monitoring for the detection of venous air embolism. J Neurosurg 1981;54:75–8.
9. Albin MS, Carroll RG, Maroon JC. Clinical considerations concerning detection of venous air embolism. Neurosurgery 1978;3:380–4.
10. Fong J, Gadalla R, Pierri MK, Druzin M. Are Doppler-detected venous emboli during cesarean section air emboli. Anesth Analg 1990;71:254–7.
11. Gibby GL. Precordial Doppler is not obsolete for venous air embolism monitoring. Anesthesiology 1988;68:829.
12. Hinman F. Atlas of urologic surgery. Philadelphia: WB Saunders, 1989:338.
13. Salo M. Fatal air embolism during transvesical prostatectomy. Ann Chir Gynaecol Fenn 1971;60:151.
14. Hofsess DW. Fatal air embolism during transurethral resection. J Urol 1984;131:355.
15. Vacanti CA, Lodhia KL. Fatal massive air embolism during transurethral resection of the prostate. Anesthesiology 1991; 74:186–7.
16. Pyron CL, Segal AJ. Air embolism: a potential complication of retrograde pyelography. J Urol 1983;130:125–6.
17. Miller RA, Kellett MJ, Wickham JEA. Air embolism, a new complication of percutaneous nephrolithotomy. J Urol 1984;90: 337–9.

An Unusual Complication of Pulmonary Artery Catheterization

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There have been many reports of flow-directed pulmonary artery catheter-related complications and malfunctions (1,2). We describe a case in which the balloon separated from the catheter during attempted removal through an introducer sheath.

Case Report

We inserted a flow-directed pulmonary artery catheter in a critically ill 35-yr-old woman. She had been admitted with acute fatty liver of pregnancy and renal failure. An introducer was placed in the right internal jugular vein and the catheter was inserted without difficulty. Two days later, we were asked to evaluate the catheter as only the middle (right ventricular) port would allow injection. Furthermore, the catheter could no longer be wedged in the pulmonary circulation. A dampened pulmonary artery tracing was present. The introducer also did not allow injection through its side port.

The decision was made to replace the catheter through the same introducer. However, resistance to withdrawal was noted. After reconfirming that the balloon was deflated, another attempt at withdrawing the catheter was successful, although there was increased resistance after the catheter tip passed into the introducer sheath. Prior chest radiographs had shown no knotting of the catheter. Upon its removal, a cursory examination gave the impression that it was intact. (The catheter tip was inspected and two bands were seen, suggesting the proximal and distal ends of an intact balloon.) Therefore, a second pulmonary artery catheter was prepared for introduction. Yet, this catheter would not advance more than 6 cm into the introducer sheath. Similarly, an attempt to advance a "J" wire was unsuccessful, leading to a decision to remove the introducer. Subsequent placement of a new introducer and pulmonary artery catheter was uncomplicated.

The introducer withdrawn from the patient was examined for occlusion. A dilator could not be passed through the introducer which was, therefore, opened linearly with a scalpel. The occlusion was found to involve a distal cylindrical blood clot with granular, sandlike material and the entire intact balloon sited more proximally within the introducer. Careful reexamination of the catheter found it also to be intact except for the missing balloon, which appeared to have separated along the "glue lines." The bands thought to have been the ends of the balloon were, in fact, indentions in the catheter where such ends are normally seated.

Discussion

The presence of a clot on the distal end of a flow-directed pulmonary artery catheter is not a new finding. Although such thrombosis has been reduced by the bonding of heparin to the catheter, this protection decreases with time (3). This woman was catheterized 48 h before the finding of the clot, a length of time sufficient to see a decrease in the effect of heparin bonding (3). Likewise, thrombogenesis is more likely in the presence of disseminated intravascular coagulation, low cardiac output, low arterial blood pressure, and congestive heart failure, all of which were present in this woman. A dampened pulmonary artery wave form suggested the presence of this clot at the catheter tip.

Mechanical factors most certainly contributed to the separation of the balloon from the catheter. The granular material found within the sheath may have been a precipitate of medications ($CaCl_2$, $NaHCO_3$) and/or blood products, or perhaps, a bonding material. Such precipitates may have narrowed the effective lumen of the introducer sheath, resulting in separation of the balloon by shearing forces.

Conceivably, the balloon may have been partially separated from the catheter before the attempt to remove the catheter. This would be most likely if

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efforts to wedge the catheter involved overinflation of the balloon. However, no instances of balloon separation from overdistention, or from any cause, have been reported previously.

Although some manufacturers of introducers recommend that the catheter and sheath always be removed as a unit, such recommendation may be excessive in that complications from catheter replacement through a sterilely maintained introducer must be compared with those of primary central venous access (this woman had disseminated intravascular coagulation). The continued use of introducers after catheter removal is commonplace and replacement of catheters through such sheaths is also widely practiced. Manufacturer's instructions included with the Baxter PA catheter kit and the Arrow percutaneous sheath introducer (both used for this case) do not advise against removal of the catheter through the introducer sheath. When excessive resistance is encountered during the removal of a catheter through an introducer sheath, however, both the introducer sheath and the catheter should always be removed simultaneously. Similarly, aspiration on a catheter during its removal should help retain any clot on the tip of the catheter, preventing its embolization.

The resistance noted in our case, although discernible, did not seem excessive until such time as the distal tip of the catheter was well within the introducer sheath. Such resistance was then believed to be due to the balloon passing by a bend in the introducer sheath. Clearly, the decision to proceed with catheter withdrawal was erroneous. Fortunately, there was no embolism of the balloon or catheter in our patient, who made a full recovery from her illness.

References

1. Sladen A. Complications of invasive hemodynamic monitoring in the intensive care unit. Curr Prob Surg 1988;25:69–145.
2. Shah KB, Tadikonda LKR, Laughlin S, El-Etr AA. A review of pulmonary artery catheterization in 6,245 patients. Anesthesiology 1984;61:271–5.
3. Mollenholt P, Eriksson I, Anderson T. Thrombogenicity of pulmonary artery catheters. Intensive Care Med 1987;13:57–9.

Bronchial Obstruction by Transesophageal Echocardiography Probe in a Pediatric Cardiac Patient

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Newer monitoring advances—despite the label "noninvasive"—often present significant risks. Transesophageal echocardiography (TEE) provides a wealth of new cardiovascular information not previously available to operating room physicians, yet requires a bulky probe inserted in juxtaposition to the patient's airway. We report a case of bronchial airway obstruction during routine use of a TEE probe in a child undergoing cardiac surgery.

Case Report

A 5.5-yr-old, 15-kg male child was brought to the operating room for elective repeat sternotomy and pulmonary arterioplasty, 14 mo after tetralogy of Fallot repair. Preoperative cardiac catheterization revealed severe residual proximal right pulmonary artery stenosis, with differential blood flow favoring the left lung in a ratio of 2.5:1.

Routine monitoring was used. A smooth, inhaled induction of anesthesia with oxygen, nitrous oxide, and halothane was followed by atraumatic orotracheal intubation. Bilateral clear breath sounds were noted, and intermittent capnography by mass spectrometry was begun with a normal waveform (Figure 1A, end-tidal carbon dioxide [$ETco_2$] = 35.6 mm Hg). After arterial and central venous cannulation were completed, a Hewlett-Packard, 5-MHz, model 21362A TEE probe mounted on a 9-mm-diameter gastroscope was passed into the esophagus under direct vision with little resistance. Within 1 min, the mass spectrometry system cycled, displaying an abnormal capnographic waveform (Figure 1B, $ETco_2$ = 12.1 mm Hg). Over the next 2 min, oxygen saturation decreased from 97% to 61%, and the child became progressively cyanotic and bradycardic (heart rate decreased from 100 to 55 beats/min). Before oxygen desaturation, both arterial systolic and mean central venous pressures remained near preinduction levels (80 and 8 mm Hg, respectively); only after desaturation occurred did arterial systolic blood pressure fall to roughly 50 mm Hg. Auscultation of the chest revealed no left-sided breath sounds despite withdrawing the endotracheal tube several centimeters. An endotracheal catheter passed without difficulty. After removal of the TEE probe, breath sounds returned bilaterally and oxygen saturation quickly reverted to baseline; blood pressure and heart rate increased rapidly and had returned to preinsertion levels within 1 min of probe removal. The next cycled capnograph noted hypercapnia, following relief of an apparent airway obstruction, which blood gas analysis corroborated. A second attempt to introduce the TEE probe resulted in similar recurrence of the obstruction, oxygen desaturation, bradycardia, and a decrease in $ETco_2$; therefore, TEE monitoring was abandoned.

Discussion

Although technological progress has yielded smaller ultrasonic probes, the transesophageal echocardiography probe is significantly larger than most other devices placed in the esophagus by the anesthesiologist. Frequently instrumented, the esophagus provides an expandable internal conduit for stethoscopes, electrocardiogram leads, temperature probes, or lower esophageal sphincter monitors; however, the largest of these monitors to date is the TEE probe.

Complications have rarely been associated with TEE in either the operating room, catheterization suite, or intensive care unit, although pediatric experience has been minimal. Of 11 recent reports describing various uses of the TEE, only two specifically pertain to children less than 17 yr old (1,2). Complications have occurred in both pediatric and adult patients regardless of anesthesia used for probe placement, including general endotracheal anesthe-

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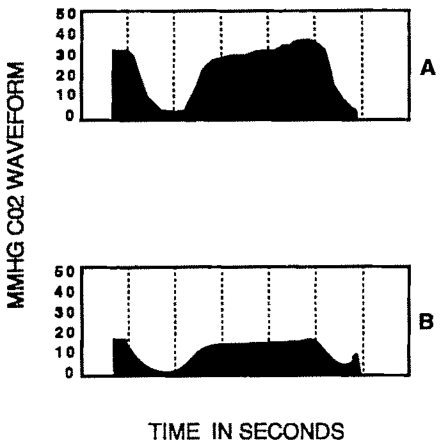

Figure 1. (A) Initial postinduction capnograph confirmed adequate ventilation before TEE insertion ($ETco_2$ = 35.6 mm Hg). (B) Immediate post-TEE insertion capnograph reflects severe mainstem bronchus obstruction with hypocapnia ($ETco_2$ = 12.1 mm Hg).

sia (1–5), intravenous sedation (6–9), and topical anesthesia alone (10).

The earliest study in the use of pediatric TEE used the Diasonics 3.5-MHz probe, measuring 35 × 15 × 16 mm at the tip and mounted on a 9-mm-diameter gastroscope (1). Cyran et al. inserted the probe successfully in 18 of 19 children between the ages of 7.5 and 16 yr during surgery for congenital heart disease. Complications identified in this study included inability to pass the TEE probe (1 patient), pharyngeal pain (1 patient), endoscopically confirmed esophageal erythema (2 patients), and hypopharyngeal bleeding (1 patient). Cyran et al. also included one patient in their study, using the Hewlett-Packard 5.0-MHz TEE probe (same model as in our report) measuring 28 × 10 × 14 mm at the tip and mounted on a 9–10-mm gastroscope, and noted no apparent complications.

One recent study used a smaller European Aloka 5.0-MHz pediatric TEE probe measuring 7 × 8 mm and mounted on a 5-mm gastroscope (2). No complications were noted in 25 children between the ages of 1 and 14.8 yr and weighing 6.5–52 kg who were studied intraoperatively.

Although some studies report no complications with TEE placement (2,3), a review of the use of Diasonics and Hewlett-Packard probes in the adult population reveals numerous other potential TEE complications including transient vocal cord paralysis (4), tachy- and brady-dysrhythmias (5,7,8), possible splenic injury (5), sore throat (8), seizure, vomiting, hypotension (9), and inability to place or remove the probe (1,6,9,10). Authors also alluded to potential, but as yet unreported, complications such as esophageal perforation and heat damage from the radiating probe (1,8).

It seems intuitive that the use of a larger "adult" TEE probe would increase the risk of airway obstruction and probably many of the above-listed complications in the pediatric population. Pediatric patients may be more at risk for airway obstruction because of the relative size of the probe-distended esophagus to adjacent airway structures and the relative compliance of the latter.

In the case we have reported, the child was at added risk because of altered anatomy and physiology resulting from his underlying pulmonary artery distortion and previous surgery. Placement of the TEE probe apparently compressed the left mainstem bronchus: an event possibly contributed to by surgical scarring and immobility of mediastinal structures. Although the right lung continued to be ventilated (as confirmed by auscultation), its perfusion was already severely diminished by preexistent right pulmonary artery stenosis (documented in preoperative catheterization). The sudden decrease in $ETco_2$ seen on capnography reflected a substantial decrease in ventilation/perfusion ratio resulting from ventilatory obstruction of the left lung—the only lung receiving significant perfusion. If a major vascular obstruction had occurred (e.g., aorta or left pulmonary artery), deterioration of hemodynamic parameters would have likely preceded desaturation and cyanosis rather than followed them as a consequence of hypoxia as seen here. Even though a mass spectrometry-based $ETco_2$ monitor only intermittently sampled the patient's exhaled gases, it was the first indicator to warn of poor ventilation—minutes before decreasing oxygen saturation, cyanosis, and hemodynamic changes were noted.

Although our institution has used the adult-sized TEE probe in children weighing as little as 13 kg, we suggest that the potential risks of airway or vascular obstruction be weighed against the value of information obtained in small children, especially in those with previous intrathoracic surgery. In addition, once a TEE probe has been placed, other monitors such as esophageal stethoscopes and temperature probes could further enlarge esophageal diameter and might increase the risk of obstructing intrathoracic structures. Although a mainstem bronchus was the likely obstruction in this patient, midline vascular structures (e.g., aorta or pulmonary vessels) likewise could conceivably be compressed by TEE probe placement.

The case we have reported points out the potential for airway obstruction and cardiovascular compromise when large TEE probes are used in small children and emphasizes the need for development and availability of small TEE probes for use in this population. It is reassuring that so few severe complications have been reported during the routine use of

TEE probes in all populations despite lengthy esophageal placement (typically throughout entire procedures) and during the anticoagulation required for most cardiac procedures.

References

1. Cyran SE, Kimball TR, Meyer RA, et al. Efficacy of intraoperative transesophageal echocardiography in children with congenital heart disease. Am J Cardiol 1989;63:594–8.
2. Stumper OF, Elzenga NJ, Hess J, Sutherland GR. Transesophageal echocardiography in children with congenital heart disease: an initial experience. J Am Coll Cardiol 1990;16:433–41.
3. Smith JS, Cahalan MK, Benefiel DJ, et al. Intraoperative detection of myocardial ischemia in high-risk patients: electrocardiography versus two-dimensional transesophageal echocardiography. Circulation 1985;72:1015–21.
4. Cucchiara RF, Nugent M, Seward JB, Messick JM. Air embolism in upright neurosurgical patients: detection and localization by two-dimensional transesophageal echocardiography. Anesthesiology 1984;60:353–5.
5. Cahalan MK. Transesophageal echocardiography: should I be using it? In: Fortieth annual refresher course lectures and clinical update program. New Orleans, Louisiana: American Society of Anesthesiologists, 1989: lecture 125.
6. Schluter M, Langenstein BA, Polster J, et al. Transesophageal cross-sectional echocardiography with a phased array transducer system: technique and initial clinical results. Br Heart J 1982;48:67–72.
7. Geibel A, Behroz A, Przewolka U, et al. Is transesophageal echocardiography a risk for patients with cardiac disease? J Am Coll Cardiol 1988;11:219A.
8. Seward JB, Khandheria BK, Oh JK, et al. Transesophageal echocardiography: technique, anatomic correlations, implementation, and clinical applications. Mayo Clin Proc 1988;63:649–80.
9. Pearson AC, Castello R, Labovitz AJ. Safety and utility of transesophageal echocardiography in the critically ill patient. Am Heart J 1990;119:1083–9.
10. Zenker G, Erbel R, Kramer G, et al. Transesophageal two-dimensional echocardiography in young patients with cerebral ischemic events. Stroke 1988;19:345–8.

Difficult Endotracheal Intubation in a Patient With Tumoral Calcinosis

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Tumoral calcinosis is a rare, benign tumor with an obscure etiology. The disease was first described by Duret in 1899, and Inclan et al. gave the lesion its name in 1943 (1). Clinically, tumoral calcinosis usually presents as multiple soft tissue masses adjacent to the large joints, which radiologically appear as lobulated calcifications (2). Joint motion is generally unaffected, but the mass may enlarge and inhibit muscle function.

The recommended treatment is early and complete excision (3–5) because of the tendency of the masses to recur after incomplete excision. We recently provided anesthetic management for two brothers with tumoral calcinosis and encountered difficult tracheal intubation in the elder one. Many of the anesthetic implications of this disease are illustrated by this case.

Case Report

A 24-yr-old man was admitted to our hospital for surgical excision of large, painful masses in his joints (Figure 1). He had had the multiple masses since childhood. The masses were diagnosed as tumoral calcinosis as the result of radiologic examination and biopsy of the masses 5 yr previously. The size of the masses had increased despite phosphate deprivation therapy, and ulcers had developed over the masses 1 yr before admission. The patient was poorly developed (152 cm tall and weighing 42 kg) and was mentally retarded; therefore, preoperative respiratory function tests were not carried out. He had a satisfactory mouth opening, but his neck flexion and extension were limited. He did not have symptoms related to the respiratory system except snoring. He had had no prior anesthesia except local infiltration anesthesia for biopsy of the calcified mass and treatment of dental caries.

Preoperative laboratory data revealed normal serum calcium, alkaline phosphatase, and parathyroid hormone levels. Elevated phosphorus, elevated acid phosphatase, low serum choline-esterase, elevated total protein, mild microcytic anemia, and increased C-reactive protein were apparent. Radiographic examination revealed multinodular calcific masses in the periarticular subcutaneous soft tissues (Figure 1).

The patient was scheduled for left renal biopsy and resection of the mass around his left shoulder, which was one of the largest tumors. He was given atropine, 0.5 mg, and hydroxyzine, 50 mg, intramuscularly, 30 min before induction of anesthesia. Thiopental, 250 mg, and succinylcholine, 40 mg, were administered intravenously to facilitate orotracheal intubation, but the airway could only be maintained with great difficulty. An attempt to visualize the larynx was unsuccessful owing probably to his limited neck extension and other anatomic abnormalities. The epiglottis could not be seen. Anesthesia was then discontinued and the operation was deferred for further evaluation of the airway.

Two days later, radiologic examination of the airway showed tumorous calcification on the hyoid bone and calcifications on the epiglottis, hyothyroid ligament, and cervical intervertebral joints (Figure 2). Fiberscopic examination revealed an omega-shaped deformity of the epiglottis, which was tucked into the subglottic space at the inspiratory phase. These abnormalities apparently had produced great difficulty in maintaining an airway and visualizing the larynx.

Two weeks after the first anesthesia, the patient was scheduled to undergo the same operations mentioned above. Droperidol, 5.0 mg IV, fentanyl, 0.1 mg IV, supplemental oxygen, and topical anesthesia were administered. An awake endotracheal intubation was performed with the aid of a fiberscope through an endotracheal tube (8.0 mm inside diameter) in the oropharynx. The epiglottis was visualized easily. The trachea was intubated by maneuvering

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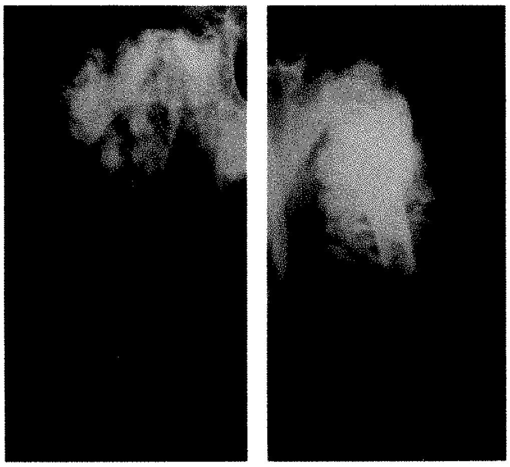

Figure 1. Conventional roentgenogram of the left shoulder (*right*) and right hip (*left*) of the elder brother showing extensive periarticular lesions.

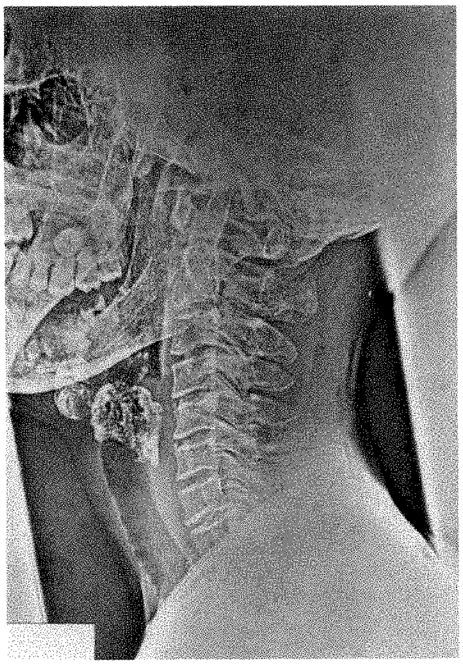

Figure 2. Lateral xeroradiograph of the neck of the elder brother showing tumorous calcification on the hyoid bone, epiglottis, hyothyroid ligament, and cervical intravertebral joints.

the tip of the fiberscope around the epiglottis and into the trachea. General anesthesia was induced with 2% enflurane and nitrous oxide in 40% oxygen, and ventilation was controlled. Resection of the mass around the left shoulder and an open biopsy of the left kidney were performed. The subsequent anesthetic and postoperative course was uneventful.

A younger brother, 19 yr old, with the same condition was later anesthetized without difficulty. He had no tumorous calcification in the airway.

Discussion

About 200 cases of tumoral calcinosis have been reported in the literature: it occurs in otherwise healthy individuals in the first and second decade of life (5,6). The condition occurs much more frequently in blacks than whites (7). Only about 10 cases have been reported in Japan. Although transmission from parents to children has never been established, the sibling presentation rate is approximately 30% (8). Our patients show one of the typical courses of this disease (9).

An inborn error of phosphorous metabolism may be a cause of this disease (10,11). Some patients have shown improvement when receiving a low-calcium/low-phosphorus diet and when given large doses of aluminium hydroxide antacids (10,11). However, this form of therapy has not been used widely and remains controversial (5,12). Treatment of tumoral calcinosis is primarily surgical (3–5).

The anesthetic implication is that tumoral calcinosis involves the patient's airway, even though this is rare. It seems that the calcifications on the corpus of hyoid bone, hyothyroid ligament, and cervical intervertebral joints made visualization of the larynx in our elder patient impossible. Several factors may cause difficult endotracheal intubation including forward displacement of the larynx and upper teeth and backward displacement of the tongue (13). In our elder patient, tumorous calcification on the corpus of hyoid bone caused a backward displacement of his tongue and immobility of his laryngeal tissues. The cervical calcification affected the cervical vertebrae, producing a fixed flexion deformity, which prevented adequate extension of the atlanto-occipital joint and resulted in anterior displacement of the larynx (14).

According to a grading of difficult tracheal intubations made by Cormack and Lehane (13), our elder patient is a grade 4, in which not even the epiglottis can be seen during laryngoscopy. To intubate the trachea, a fiberoptic bronchoscope was used, which revealed an omega-shaped deformity of the epiglottis. The epiglottis was tucked into the subglottic space at the inspiratory phase, which seemed to cause snoring and difficulty in maintaining his airway during induction of anesthesia.

This case suggests that a patient undergoing surgical resection of tumoral calcinosis under general anesthesia may present the potential for a difficult tracheal intubation.

References

1. Inclan A, Leon P, Camejo MG. Tumoral calcinosis. JAMA 1943;121:490–5.

2. Resnik CS. Tumoral calcinosis. Arthritis Rheum 1989;32: 1484–6.
3. Buschmann WR, Myers W, Sager G. Tumoral calcinosis: case presentation and review. Orthop Rev 1989;18:440–2.
4. Seimon LP. Tumoral calcinosis: a surgical problem. J Pediatr Orthop 1982;2:409–15.
5. Heydemann JS, McCarthy RE. Tumoral calcinosis in a child. J Pediatr Orthop 1988;8:474–7.
6. Bostrom B. Tumoral calcinosis in an infant. Am J Dis Child 1981;135:246–7.
7. Veress B, Malic MOA, Hassan AM. Tumoral lipocalcinosis: a clinicopathological study of 20 cases. J Pathol 1976;119:113–8.
8. Barton DL, Reeves RJ. Tumoral calcinosis: report of three cases and review of the literature. Am J Roentgenol Radium Ther Nucl Med 1961;86:351–8.
9. Kirk TS, Simon MA. Tumoral calcinosis: report of a case with successful medical management. J Bone Joint Surg 1981;63-A: 1167–9.
10. Mozaffarian G, Lafferty FW, Pearson OH. Treatment of tumoral calcinosis with phosphorus deprivation. Ann Intern Med 1972;77:741–5.
11. Mitnick PD, Goldfarb S, Slatopolsky E, Lemann J, Gray RW, Agus ZS. Calcium and phosphate metabolism in tumoral calcinosis. Ann Intern Med 1980;92:482–7.
12. Waletynowicz JE, Mahoney MD, Saldana MJ. Tumoral calcinosis: case report with treatment failure. Orthop Rev 1989;18: 687–90.
13. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia 1984;39:1105–11.
14. Nichol HC, Zuck D. Difficult laryngoscopy—the "anterior" larynx and the atlanto-occipital gap. Br J Anaesth 1983;55: 141–4.

Anesthetic Care of Patients With Crigler-Najjar Syndrome

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Crigler-Najjar syndrome is a rare inherited deficiency of bilirubin uridine diphosphate glucuronyl transferase, characterized by lifelong unconjugated hyperbilirubinemia. Children with this syndrome are at risk for bilirubin-induced encephalopathy (kernicterus). Various drugs as well as metabolic perturbations characteristic of the perioperative period may exacerbate hyperbilirubinemia acutely in patients with Crigler-Najjar syndrome. A rationale for safe anesthetic management of these patients is outlined in this report.

Case Report

The patient, a 7-yr-old, 16-kg boy with Crigler-Najjar syndrome, was small for his age (16th percentile). His neurologic development was normal. His medical regimen included intensive home phototherapy (as much as 20 h/day), which severely restricted his lifestyle.

The patient underwent two general anesthetics, first for restorative dentistry and then for orthotopic liver transplantation. Before both procedures, the child was alert and cooperative, and obviously jaundiced. His airway examination was normal, lung fields were clear to auscultation, and no cardiac murmurs were heard. Preoperative laboratory values included hematocrit 27%, white blood cell count 9100/mm^3, platelet count 229,000/mm^3, prothrombin time 14.6 s, partial thromboplastin time 45.4 s, and fibrinogen 161 mg/dL. Total bilirubin was 12 mg/dL (normal up to 1 mg/dL).

Because of extensive caries and gingivitis, the child was believed at risk for oral infections after immunosuppression. For this reason, he was scheduled for dental restoration before liver transplantation. For dental restoration, anesthesia was induced by inhalation of halothane and nitrous oxide. Atracurium was used for neuromuscular blockade. Anesthesia was maintained with isoflurane and morphine. At the end of the case, neuromuscular blockade was reversed with glycopyrrolate and IV neostigmine. The child's usual regimen of phototherapy was maintained with four banks of bilirubin lights in the operating and recovery rooms. Recovery was uneventful, and he was discharged home 4 h after the procedure.

Liver transplantation was done 3 mo after the first procedure. His physical status and laboratory values were unchanged. Because the patient had an episode of emesis just before surgery, he received a rapid sequence induction of anesthesia, 50 mg thiopental and then 20 mg succinylcholine IV. His trachea was intubated without difficulty, and anesthesia was maintained with isoflurane and fentanyl, and paralysis with vecuronium. Arterial and central venous pressures were monitored via cannulas inserted in the radial artery and internal jugular vein. The patient was stable throughout all phases of surgery, including the anhepatic phase which lasted 37 min. Venovenous bypass was not used. Bilirubin lights were used during the preoperative period and during surgery so as not to disrupt the patient's regimen.

After reperfusion of the donor liver, metabolic acidosis persisted, an indication of poor graft function, and the patient required 110 mEq of sodium bicarbonate over 4 h to maintain normal arterial pH. The patient's liver was actively metabolizing acid by the time of transport to the intensive care unit. Total fluid replacement for the 11-h procedure consisted of 10,300 mL crystalloid, 450 mL packed red cells, 600 mL fresh frozen plasma, and 750 mL 5% albumin for an estimated blood loss of 1000 mL, urine output of 6200 mL, and nasogastric output of 2000 mL. He was transported to the intensive care unit without event, and the trachea was extubated 3 h after arrival. The postoperative course was complicated by a mild rejection episode, successfully treated with OKT3, a monoclonal antibody directed against the T-cell CD3 receptor. He was discharged home 3 wk after transplantation.

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Discussion

Congenital familial nonhemolytic jaundice with kernicterus was first reported by Crigler and Najjar in 1952 (1). Later, Crigler-Najjar syndrome of two distinct types was described (2). The hyperbilirubinemia of type 2 patients is responsive to barbiturate therapy and is generally less severe than type 1, although kernicterus can occur. Kernicterus is a distinct risk of type 1 disease and often occurs before the age of 20 yr (3).

Normally, excretion of bilirubin in bile requires bilirubin metabolism to water-soluble derivatives, mostly glucuronides, via the enzyme uridine diphosphate-glucuronyl transferase. Glucuronide derivatives are efficiently excreted in bile. At low serum concentrations of bilirubin, almost all bilirubin is bound to plasma albumin. In patients with Crigler-Najjar syndrome, free bilirubin (not bound to albumin) is thought to be the source of kernicterus, although the exact mechanism of central nervous system damage is not known.

The mainstay of therapy for patients with type 1 disease is phototherapy with visible light to reduce bilirubin levels. Low-pressure mercury or tungsten fluorescent tubes are used as the light source because they emit light in a wavelength (450 nm) that is absorbed by bilirubin (4). The photochemical reactions induced by light therapy change bilirubin into more polar compounds, which can be excreted directly without conjugation. Phototherapy may become less effective as a child matures because of lack of cooperation, thicker skin, and a decreased surface-to-mass ratio (5). Phototherapy is painless and free of side effects if properly used; however, intensive phototherapy severely limits lifestyle.

A new drug, tin protoporphyrin, may represent a second therapeutic option in the future. The drug is a heme-oxygenase inhibitor and completely halts catabolism of heme to bilirubin. In the animal model of Crigler-Najjar syndrome (the Gunn rat), tin protoporphyrin effectively blocks the usual elevation of serum bilirubin (6). Tin protoporphyrin has been used in only one patient with Crigler-Najjar syndrome (7), so that its effectiveness in humans is not yet known (8).

For acute exacerbations of disease associated with trauma or other superimposed stresses, both plasmapheresis and plasma exchange (9,10) have been used successfully to lower levels of free bilirubin.

Unfortunately, phototherapy and plasmapheresis represent only temporary treatments for patients with Crigler-Najjar syndrome. Liver transplantation is the only permanent therapy available. Liver transplantation was first reported as a cure for Crigler-Najjar syndrome in 1986 (3) and is considered an option when phototherapy fails or severely limits a patient's emotional or social development. In the first case report, the rapid efficacy of liver transplantation was demonstrated by the dramatic fall in serum bilirubin from 26 to 2 mg/dL within 1 day of the procedure. In our patient, serum bilirubin fell from 12 to 1.2 mg/dL despite transient graft dysfunction. Liver transplantation should occur before the child has significant neurologic damage. In one patient, neurologic dysfunction did not improve after transplantation (5).

In the anesthetic management of children with Crigler-Najjar syndrome, bilirubin phototherapy lights should be available and used until the time of surgery if that is the child's routine. Since unexpected delays may disrupt the usual therapeutic schedule, lights should be available for the preoperative waiting area, operating room, and recovery room. Lights are ineffective if the child is clothed.

Fasting should be minimized because this stress is known to increase bilirubin levels (2). Children with Crigler-Najjar syndrome and intercurrent infectious illness are at risk of acute exacerbations of hyperbilirubinemia (11) without the added stress of a surgical procedure. For this reason, it seems prudent to postpone elective surgery until the child has recovered from an infection.

Bilirubin bound to albumin may be able to cross the blood-brain barrier under conditions that abnormally increase blood-brain barrier permeability, such as severe hypertension or hypercarbia. In animal models, respiratory acidosis particularly predisposes to bilirubin deposition in brain (12). Under hyperosmolar conditions, albumin-bound bilirubin may cross the blood-brain barrier (13).

Highly protein-bound drugs may displace bilirubin from albumin. Sulfonamides were associated with kernicterus in premature infants decades ago (14). In this setting of an immature blood-brain barrier, sulfonamide displacement of bilirubin from albumin is the cause of kernicterus (15). Some cephalosporins are also characterized by avid protein binding and may exacerbate free hyperbilirubinemia (16). Intravenous contrast dyes may also displace bilirubin from albumin (17). Drugs that avidly bind protein in vitro, but have not been studied in vivo, should therefore be avoided in patients with Crigler-Najjar syndrome (17). A list of (nonanesthetic) drugs thought to exacerbate hyperbilirubinemia is referenced (17). Fortunately, most commonly used anesthetics are not characterized by avid protein binding.

Morphine is metabolized by a different glucuronyl transferase enzyme system than that which is deficient in Crigler-Najjar syndrome. Morphine, therefore, can be used safely in these patients. Barbiturates, neuromuscular blocking agents, and inhaled anesthetics are safe options in patients with Crigler-

Najjar syndrome. Although inhaled anesthetics are known to bind protein (18), displacement of other drugs (or bilirubin) from protein binding sites has not been demonstrated with anesthetic gases.

Many drugs have not been tested for their abilities to displace bilirubin or other drugs from protein binding sites. Consultation with a clinical pharmacologist is recommended if the protein-binding characteristics of a particular drug are of concern.

In summary, patients undergoing liver transplantation for any reason may be subjected to an extremely long surgical procedure. In addition, the hepatic graft may not function immediately or at all. For these reasons it seems prudent to continue aggressive phototherapy of patients with Crigler-Najjar syndrome until the transplanted liver is functioning well. Preoperative cephalosporins are often used before liver transplantation, but for patients with Crigler-Najjar syndrome alternative antibiotic prophylaxis is recommended (for example, ampicillin and gentamicin). Hyperosmolality, hypercarbia, and acidosis should be avoided. Bilirubin lights should be available for the entire perioperative period. Narcotics, barbiturates, inhaled anesthetics, and muscle relaxants may be used safely in these patients.

We thank Dr. Tony McDonagh for his assistance.

References

1. Crigler JF Jr, Najjar VA. Congenital familial nonhemolytic jaundice with kernicterus. Pediatrics 1952;10:169–79.
2. Arias IM, Gartner LM, Cohen M, Ben Ezzer J, Levi AJ. Chronic nonhemolytic unconjugated hyperbilirubinemia with glucuronyl transferase deficiency. Am J Med 1969;47:395–409.
3. Kaufman SS, Wood RP, Shaw BW Jr, et al. Orthotopic liver transplantation for type I Crigler-Najjar syndrome. Hepatology 1986;6:1259–62.
4. McDonagh AF, Palma LA, Lightner DA. Blue light and bilirubin excretion. Science 1980;208:145–51.
5. Pett S, Mowat AP. Crigler-Najjar types I and II. Clinical experience—King's College Hospital 1972–1978. Phenobarbitone, phototherapy and liver transplantation. Mol Aspects Med 1987;9:473–82.
6. Sisson TRC, Drummond GS, Samonte D, Calabio R, Kappas A. Sn-protoporphyrin blocks the increase in serum bilirubin levels that develop postnatally in homozygous Gunn rats. J Exp Med 1988;167:1247–52.
7. Rubaltelli FF, Guerrini P, Reddi E, Jori G. Tin-protoporphyrin in the management of children with Crigler-Najjar disease. Pediatrics 1989;84:728–31.
8. McDonagh AF. Tin-protoporphyrin in the management of children with Crigler-Najjar disease (letter). Pediatrics 1990;86: 151–2.
9. Sherker AH, Heathcote J. Acute hepatitis in Crigler-Najjar syndrome. Am J Gastroenterol 1989;82:883–5.
10. Mooney RA, Smith CH, Zarkowsky HS. Free bilirubin measurements in a patient with Crigler-Najjar after crush injury. J Pediatr 1983;103:262–5.
11. Mowat AP. Liver disorders in children: the indications for liver replacement in parenchymal and metabolic diseases. Transplant Proc 1987;19:3236–41.
12. Bratlid D, Cashore WJ, Oh W. Effect of acidosis on bilirubin deposition in rat brain. Pediatrics 1984;73:431–4.
13. Hansen TWR, Oyasoeter S, Stiris T, Bratlid D. Effects of sulfisoxazole, hypercarbia, and hyperosmolality on entry of bilirubin and albumin into brain regions in young rats. Biol Neonate 1989;56:22–30.
14. Silverman WA, Andersen DH, Blanc WA, Crozier DN. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics 1956;18:614–24.
15. Odell GB. The dissociation of bilirubin from albumin and its clinical implications. J Pediatr 1959;55:268–79.
16. Stutman HR, Parker KM, Marks MI. Potential of moxalactam and other new antimicrobial agents for bilirubin-albumin displacement in neonates. Pediatrics 1985;75:294–8.
17. Brodersen R. Free bilirubin in blood plasma of the newborn. Effects of albumin, fatty acids, pH, displacing drugs and phototherapy. Appendix: a provisional survey of the bilirubin-displacing effect of 150 drugs. In: Stern L, ed. Intensive care in the newborn. Volume 2. New York: Masson, 1978:331–45.
18. Mashimo T, Kamaya H, Ueda I. Anesthetic-protein interaction: surface potential of bovine serum albumin estimated by a pH-sensitive dye. Mol Pharmacol 1986;29:149–54.

Letters to the Editor

End-Systolic Pressure-Volume Relationship and Arterial Elastance: The Optimal Method to Evaluate Myocardial Contractile Effects of Anesthetic Agents?

To the Editor:

Dr. Mulier and colleagues (1) add new evidence to the available data suggesting a negative inotropic action of propofol. Their study also demonstrates that the major effect of propofol on hemodynamics is explained by changing loading conditions. However, their methodology deserves some comment.

The authors provide an analysis of ventriculoarterial interactions as described by Sagawa et al. (2). Therefore, arterial elastance (Ea) and end-systolic pressure-volume relations (ESPVR) are computed and their slopes are compared. The concept of ESPVR is based on the "time varying elastance model" of the ventricle. Consequently, an exact definition of the timing of "end-systole" is required in plotting an ESPVR. If end-systole is referred to the echocardiographic end-systolic volume, complete ventricular ejection is assumed and pressure at the corresponding time should be registered (2). This pressure should be measured at aortic valve closure and thus at the dicrotic notch of an ascending aortic pressure trace because of differences in timing between radial artery and ascending aortic pressure waves. Systolic radial artery pressure may differ importantly from ascending aortic pressure at aortic valve closure, especially if the study drug provokes arterial vasodilation.

The linearity of ESPVR probably is lost in the low-pressure range because of reflex mechanisms. Plotting stroke work versus end-diastolic volume yields better linearity in the lower pressure range (3). Extrapolation of the ESPVR to the zero pressure intercept yields Vd. The accuracy of determination of Vd thus depends on the linearity of the relationship. Ideally this linearity should be tested with linear regression analysis. A second ESPVR under propofol or thiopental is constructed on the basis of only one point: the same Vd is used. Vd however has been described to change with varying loading conditions or contractility (2).

The slopes of both ESPVR are obtained from parts of the ESPVR lying far from the pressure range where measurements were actually performed and thus are highly dependent on accurate extrapolation.

Finally, comparison of Ea or ESPVR under different conditions can only be valid if heart rate is fairly constant (2). It is well known that thiopental influences heart rate in a different way than propofol. Indeed in the study under consideration, group D heart rate increases with thiopental whereas in group C heart rate is not significantly changed. Although group means of heart rate are not different, both groups display a different trend during therapy. This differing trend is explained by differences in baroreflex activity induced by thiopental and propofol, which probably also affects contractility and the conclusions of Mulier et al (1).

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References

1. Mulier JP, Wouters PF, Van Aken H, et al. Cardiodynamic effects of propofol in comparison with thiopental: assessment with a transesophageal echocardiographic approach. Anesth Analg 1991;72:28–35.
2. Sagawa K, Maughan L, Suga H, Sunagawa, K. Cardiac contraction, and the pressure-volume relationship. New York: Oxford University Press, 1988.
3. Little WC, Cheng C-P, Mumma M et al. Comparison of measures of left ventricular contractile performance derived from pressure-volume loops in conscious dogs. Circulation 1989;80:1378–87.

Sacrococcygeal Teratoma and Venous Shunting Through a Tumor: Biological Evidence

To the Editor:

Bonds et al. (1) report 48 cases of sacrococcygeal teratoma and suggest that high fetal mortality was probably due to the tumor acting as an arteriovenous fistula resulting in high-output cardiac failure. The following case provides evidence that this hypothesis is valid.

A 21-yr-old woman (gravida 1) with an unremarkable medical history was referred to us for routine sonography examination at 22-wk gestation. The sonogram showed a pedicled mass, 55 mm in diameter, arising from the sacrococcygeal region. There was no intrapelvic extension, and the placenta was normal. A repeat sonogram at 33 wk showed that the tumor had grown, and because placentomegaly, hydramnios, and hydrops had developed, the decision was made to do a cesarean section. Preoperative sonography revealed a large feeder vessel, 7 mm in diameter, three times larger than the iliac artery. All signs indicated that blood had been diverted from the heart toward the tumor. The resulting loss of circulation was controlled by clamping.

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Anasarca was certain because peritoneal and pleural effusions were present. The trachea was immediately intubated and ventilation was controlled. The tumor was larger than the head of the fetus. After removal, the tumor weighed 1600 g and the newborn 2100 g. Arterial blood was sampled through an umbilical artery catheter before excision of the tumor; $\mathrm{Pa}_{\mathrm{O}_2}$ was 40 mm Hg, $\mathrm{Pa}_{\mathrm{CO}_2}$ 144 mm Hg, pHa 6.8. Oxygen saturation was 34% and alkali reserve 20.7 mmol/L. After excision $\mathrm{Pa}_{\mathrm{O}_2}$ was 541 mm Hg, $\mathrm{Pa}_{\mathrm{CO}_2}$ 28 mm Hg, pHa 7.45 with 99% oxygen saturation, and alkali reserve 21 mmol/L. The infant was discharged 2 wk after the operation. Clinical examinations at 4, 6, and 12 mo revealed no cardiac or neurologic abnormalities.

This is the only reported case showing the dramatic improvement of hypoxia, hypercarbia, and acidosis by excision of the tumor. These biological values support the hypothesis that in these cases the tumor acts as a large shunt.

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References

1. Bonds SJ, Arrison MR, Schmidt KG, et al. Death due to high-output cardiac failure in fetal sacrococcygeal teratoma. J Pediatr Surg 1990;25: 1287–91.

Heart Rate and the Oculocardiac Reflex

To the Editor:

We read with interest the article by Loewinger et al. (1). As mentioned in the article, the OCR (which is trigeminal-vagal reflex) can produce bradycardia, chaotic dysrhythmias, and sinoatrial arrest. In the study, 60% of the children who received pancuronium developed bradycardia and 9% developed dysrhythmias, and 93% of the children who received atracurium developed bradycardia and 20% of them developed dysrhythmias.

We use atracurium to facilitate orotracheal intubation in our practice. We administer 20 μg/kg of atropine intravenously prophylactically to block the vagus nerve. None of our children developed OCR. It is true that after the intravenous administration of 20 μg/kg of atropine, some of the children developed higher rates than we desire, but the sinus tachycardia was not associated with any apparent side effects.

We believe that in healthy children undergoing strabismus surgery it is a safe practice to administer 20 μg/kg of atropine prophylactically to prevent OCR, and that the use of atropine to block the vagus nerve is more reliable than the use of pancuronium to prevent OCR.

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1. Loewinger J, Friedmann-Neiger I, Cohen M, Levi E. Effects of atracurium and pancuronium on the oculocardiac reflex in children. Anesth Analg 1991;73:25–8.

To the Editor:

The article by Loewinger et al. (1) states that the incidence and severity of dysrhythmias from the oculocardiac reflex (OCR) are more frequent in children receiving atracurium than in those receiving pancuronium. However, they did not include in their analysis the observation that the baseline intraoperative heart rate was markedly slower in children receiving atracurium (86 ± 20 beats/min) than in children paralyzed with pancuronium (120 ± 17). This is a statistically significant difference, and a cursory calculation between the baseline heart rates of the two groups reveals $P < 0.0001$ based on the *t*-test.

The efferent arc of the OCR is through the vagus nerve. Pancuronium has a mild to moderate vagolytic effect that usually manifests as a mild tachycardia. Atracurium has no such effect; therefore, in a patient with partial vagal blockade, the manifestations of the OCR will be less apparent. This study would have been more informative if the authors had included a third group of patients in their study who had been paralyzed with atracurium and had heart rate elevated by other pharmacologic means to a level comparable to that of the pancuronium group. We would have then known whether the exaggeration of the OCR was due to the drug itself or due to the lack of its vagolytic effects. Our personal impression is that a high resting intraoperative heart rate is the crucial factor in decreasing the severity of the OCR: a situation where the physiologic status of the patient is more important than the pharmacologic agents used.

In reviewing the study of Karhunen et al. (2) who investigated the same subject with four relaxants (tubocurarine, pancuronium, vecuronium, and alcuronium), we also note that the incidence of dysrhythmias was lowest in the group of patients with the highest heart rate who had received alcuronium followed by pancuronium. It would also have been important to note the $\mathrm{Pa}_{\mathrm{CO}_2}$ (or measured $\mathrm{P}_{\mathrm{ETCO}_2}$) as hypercarbia will lower the threshold for eliciting OCR (3).

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References

1. Loewinger J, Friedmann-Neiger I, Cohen M, Levi E. Effects of atracurium and pancuronium on the oculocardiac reflex in children. Anesth Analg 1991;73:25–8.
2. Karhunen U, Nilsson E, Brander P. Comparison of four nondepolarizing neuromuscular blocking drugs in the suppression of the oculocardiac reflex during strabismus surgery in children. Br J Anaesth 1985;57:1209–12.
3. Blanc VF, Hardy J-F, Milot J, Jacob J-L. The oculocardiac reflex: a graphic and statistical analysis in infants and children. Can Anaesth Soc J 1983;30:360–9.

In Response:

We concur with Dr. Khalil that a prophylactic dose of atropine, 20 μg/kg given intravenously immediately before orotracheal intubation, will effectively block the vagus nerve and thereby prevent or greatly lessen the incidence of the OCR in healthy children undergoing strabismus surgery. It should probably be given to all such children, irrespective of the muscle relaxant used during this surgical procedure, and we stated this conclusion in the final paragraph of our paper.

The purpose of our study, however, was to compare the incidence of this potentially dangerous reflex in children receiving atracurium and pancuronium, as this particular facet of atracurium's pharmacologic profile had not previously been reported on. We would only recommend pancuronium as the preferred muscle relaxant where the tachycardia induced by a vagus-blocking dose of atropine would be undesirable.

Drs. Goudsouzian and Ferrari are correct in pointing out the significant difference in the baseline intraoperative heart rate in the two groups, and this is clearly indicated in Table 3 and in the third paragraph of our Results.

We, too, are of the opinion that a high resting intraoperative heart rate is an important factor in decreasing the incidence and severity of the OCR and that where atracurium is used for this operation, this goal should be achieved by prophylactic intravenous atropine.

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Anaphylactic Reactions During Anesthesia

To the Editor:

To evaluate patients with suspected drug-induced anaphylactic reactions during anesthesia, we are currently studying a new test for mast-cell activation that should be helpful in investigating these life-threatening reactions. If you have a patient in whom a suspected anaphylactic reaction has developed, please obtain one serum or plasma sample as soon as possible during the reaction, then an additional sample 1 h later, and forward to me with the anesthesia records. If you have any questions, please also call (404) 248-3203.

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Bleeding Diathesis After Perioperative Ketorolac

To the Editor:

I would like to comment on the letter by Fleming and Coombs (1) that implicated ketorolac in an incident of gastrointestinal bleeding 5 days after its use in a patient receiving a full anticoagulant dose of oral coumadin. The patient had prothrombin and partial thromboplastin times of 1.5–2 times normal. No report of the bleeding time was given. The patient also admitted, after the complication occurred, that he was taking 10–14 aspirin tablets per day before his total knee reconstruction.

Ketorolac, like the other nonsteroidal antiinflammatory drugs (NSAIDs), specifically affects platelet function, mildly increasing the bleeding time from a mean of 4.9 to 7.8 min in one study (2). Ketorolac does *not* interact with heparin, nor does it affect clotting time or platelet *count* (3). Unlike aspirin, ketorolac is reversible in its effect, and hemostasis returns to normal once it is eliminated (4). Large doses (90 mg) of ketorolac have clearly resulted in significant antral ulceration (5), resulting in the 90-mg dose being withdrawn by Syntex (Syntex, personal communication). In that study (5), patients who received the equivalent of two aspirin tablets every 6 h had greater ulceration than patients receiving 30 mg of ketorolac IM every 6 h. According to Syntex, the patients in the 90-mg test group were withdrawn from the study, and treated with an H_2-antagonist for 2 wk, with complete resolution of the ulceration.

The patient described in the letter had a number of problems that may have interacted to cause his gastrointestinal bleeding. He was taking large doses of aspirin preoperatively, with an unknown effect on his gastrointestinal tract and his bleeding time. He was on a full anticoagulant dose of coumadin, rather than a dose for prophylaxis against deep venous thrombosis. He only received ketorolac for 1 day, yet the bleeding occurred 5 days after surgery. If bleeding time had still been elevated at this time, it would have probably been due to the effects of the aspirin.

Given the results of the antral ulceration study, it is interesting to speculate whether or not concomitant prophylaxis with an H_2-antagonist would have prevented the bleeding that occurred. A study testing this hypothesis has not yet been, but probably should be, done.

Although it is difficult to attribute the complication described in this patient to ketorolac, I agree with Drs. Fleming and Coombs that ketorolac should be used with caution in patients at risk for bleeding complications unless there is a clear indication for using it. The studies of ketorolac were all done in patients with no history of gastrointestinal disease, no history of bleeding disorders, and no history of chronic NSAID use. The reported complications in these studies were few, and no incidence of clinically significant bleeding occurred (6). However, with more widespread use of ketorolac in patients at greater risk for complications, we may see other such incidents that may be attributed, rightly or wrongly, to ketorolac.

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References

1. Fleming BM, Coombs DW. Bleeding diathesis after perioperative ketorolac. Anesth Analg 1991;73:235.
2. Conrad KA, Fagan TC, Mackie MJ, Mayshar PV. Effects of ketorolac tromethamine on hemostasis in volunteers. Clin Pharmacol Ther 1988;43: 542–6.
3. Spowart K, Greer IA, McLaren M, Lloyd J, Bullingham RES, Forbes CD. Haemostatic effects of ketorolac with and without concomitant heparin in normal volunteers. Thromb Haemost 1988;60:382–6.
4. Roe RL, Bruno JJ, Ellis DJ. Effects of a new nonsteroidal antiinflammatory agent on platelet function in male and female subjects. Clin Pharmacol Ther 1981;29:277.
5. Lanza FL, Karlin DA, Yee JP. A double-blind placebo controlled endoscopic study comparing the mucosal injury seen with an orally and parenterally administered new nonsteroidal analgesic ketorolac tromethamine at therapeutic and supratherapeutic doses. Am J Gastroenterol 1987;82:939.
6. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D. Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 1987;41:556–61.

To the Editor:

Drs. Fleming and Coombs (1) proposed that ketorolac may have caused a bleeding diathesis in a 65-yr-old man who underwent total knee reconstruction. On the fifth postoperative day this man had a significant upper gastrointestinal hemorrhage. He had received ketorolac only during the first postoperative day. He also was prescribed 10 mg of oral coumadin daily until his hemorrhage. Their patient had a history of taking aspirin before admission but denied any previous ulcer history.

Fleming and Coombs offer no evidence to help us understand ketorolac's role, if any, in this man's bleeding diathesis. Bleeding times, if obtained at all preoperatively and/or postoperatively, were not reported. Prothrombin and partial thromboplastin tests do not measure platelet dysfunction. The values given for these tests were consistent with coumadin administration. Bleeding can occur with coumadin when the prothrombin time is in the therapeutic range. Their patient recovered receiving only packed red blood cells and fresh frozen plasma. Platelet transfusions were apparently not necessary.

Ketorolac, as a NSAID, may cause bleeding through platelet dysfunction. These effects can be additive with other NSAIDs (such as aspirin). Is there a synergistic effect with coumadin? Ketorolac does not seem to affect the pharmacokinetics or pharmacodynamics of coumadin. Unlike the prolonged effects from aspirin, the inhibition of platelet function by ketorolac disappears within 24–48 h after the drug is discontinued.

Since its introduction, anesthesiologists have wondered if ketorolac would cause bleeding problems in the perioperative period. Fleming and Coombs consider the same question but give us no insight into the answer. We are left asking the exact same question again.

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1. Fleming BM, Coombs DW. Bleeding diathesis after perioperative ketorolac. Anesth Analg 1991;73:235.

In Response:

We appreciate the opportunity to respond to the letters from O'Hara and Horswell regarding our communication (1). Both O'Hara and Horswell are incorrect in stating that we attributed the bleeding complication in a patient on our postoperative pain service singularly to the use of ketorolac. For the record, the prior use of aspirin was unknown until the complication occurred and was treated. Unfortunately, bleeding times were not determined to help clarify the situation. Certainly an important piece of history was regrettably overlooked that might have forecast the events that followed. The patient did receive platelet transfusion during resuscitation, and we regret this omission in our communication. The intended point of the report is to illustrate how the cumulative effects of several pharmacologic agents may have led to the patient's hemorrhage, with the relatively new analgesic ketorolac being a potential contributor. The somewhat longer terminal half-life (7–9 h) of ketorolac in the elderly patient might in any event have blocked the function of any new platelets formed since the patient last took aspirin. Such an inhibition may have persisted well beyond the 24 h after the last ketorolac administration (perhaps partial effects for 3–4 half-lives). We believe this factor, together with contributory effects of surgical dilution and loss of platelets and residual aspirin-impaired platelets, may have facilitated a heightened risk with coumadin anticoagulation. We also were not trying to implicate ketorolac primarily in the gastric ulcerative process as prolonged aspirin use, nasogastric tube-induced injury, or perioperative stress might all have generated this problem; an impaired healing of a preexisting mucosal injury is difficult to speculate upon. Though platelet function was not studied, platelet counts were within the normal range at the time of the hemorrhage. Both O'Hara and Horswell correctly point out that our knowledge of ketorolac effects on bleeding time has been based on volunteers and not on patients with more complicated settings such as the case reported. There is need to individually study such issues. Is it safe to use ketorolac for 24 h when platelet inhibition will occur coincidentally with an unpredictable rate of increasing anticoagulation as seen with oral coumadin. In the final analysis we all agree that care and judgment is indicated when using drugs with platelet inhibitory effects, and we hope to call attention to the relevance of this issue with use of the highly effective new analgesic ketorolac.

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Reference

1. Fleming BM, Coombs DW. Bleeding diathesis after perioperative ketorolac. Anesth Analg 1991;73:235.

A Potential Complication of Lightwand-Guided Intubation

To the Editor:

Transillumination of the trachea is a valuable method of achieving tracheal intubation, and this technique has been made easier by the ready availability of "lightwands" such as the Flexilum surgical light (Concept, Inc., Clearwater, Fla.) (1). We recently had a case in which the lens of the Flexilum bulb became detached even though prior inspection had suggested that it was secure. Detachment of the whole bulb has been reported previously (2), and it has been suggested that this is related to reuse of the equipment (3). It is not known how many times this particular item had been used previously, but it is likely that previous trauma had damaged the bulb. It must be remembered that this device was not originally intended as an endotracheal intubating stylet. We wish to remind readers of this potential complication and suggest that its use for this purpose be reconsidered.

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References

1. Hammer M, Garry B. Transillumination of the trachea with Flexilum (letter). Anesth Analg 1985;64:91–2.
2. Stone DJ, Stirt JA, Kaplan MJ, McLean WC. A complication of lightwand-guided nasotracheal intubation. Anesthesiology 1984;61:780–1.
3. Williams RT, Stewart RD. Transillumination of the trachea with a lighted stylet (letter). Anesth Analg 1986;65:542–3.

Combined Spinal-Epidural Anesthesia Using the CSEN

To the Editor:

A special needle (combined spinal-epidural needle; CSEN) was designed to facilitate the combined spinal-epidural anesthesia technique (Figure 1). The needle is composed of an 18-gauge epidural needle brazed to a 20-gauge guide spinal needle.

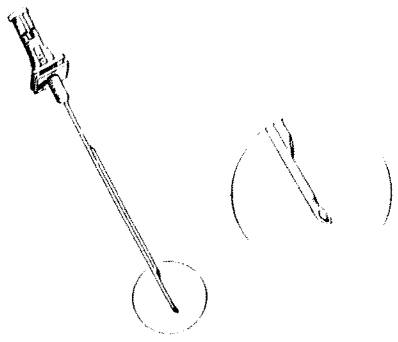

Figure 1. Combined spinal-epidural needle.

Ten parturients (21–32 yr old; ASA physical status I) were included. Informed consent was obtained for the anesthetic procedure. One thousand milliliters of lactated Ringer's solution, normal saline, or haemacel was infused before starting the procedure. A CSEN was inserted after a local anesthetic was injected at the L3-4 interspace.

After reaching the epidural space with the epidural part of the CSEN using the loss-of-resistance technique, a 25-gauge spinal needle was pushed further (approximately 1.5 cm) to reach the spinal space. The spinal needle was inserted through the spinal guide tube that was brazed to the epidural needle. The distance between the tips of the spinal guide needle and the epidural needle is approximately 1 cm, so 0.5–1 cm was needed to reach the dura from the level of the epidural needle.

After injecting a spinal solution (3 mL of 0.5% heavy bupivacaine) into the subarachnoid space, the 25–26-gauge spinal needle was withdrawn, and an epidural catheter was inserted through the epidural part of the CSEN into the epidural space. The catheter is needed in case another injection of local anesthetic is needed and an inadequate spinal anesthesia is obtained, and for postoperative analgesia with morphine.

In all the parturients, the insertion of the CSEN was done without any problem. The feeling of protruding the CSEN through the skin is a little bit different from the feeling with the usual epidural needle, and this is because of the spinal guide needle that is attached to it approximately 1 cm proximal to the tip of the epidural part of the CSEN. Some pressure is felt when pushing the spinal part through the skin. Afterwards the feeling is almost the same as for the usual epidural needle, and the epidural space is easily obtained through the loss-of-resistance technique or the hanging-drop technique. While in the epidural space with the epidural part of the CSEN, an epidural catheter can be pushed or the spinal needle can be inserted through the spinal guide needle into the spinal space until cerebrospinal fluid is obtained (Figure 2).

In three patients, cerebrospinal fluid was not obtained even though an anesthetic solution was injected through the spinal needle and spinal anesthesia was accomplished.

Acceptance of the procedure was very good in all the 10

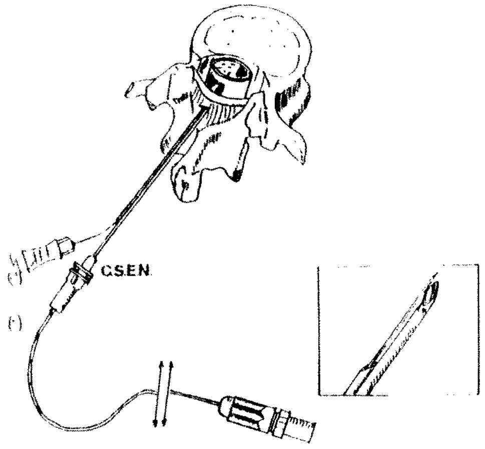

Figure 2. Combined spinal-epidural needle in place with a spinal needle introduced through its spinal guide tunnel into the spinal space and an epidural catheter in the epidural space. The tips of the CSEN and the spinal needle are magnified.

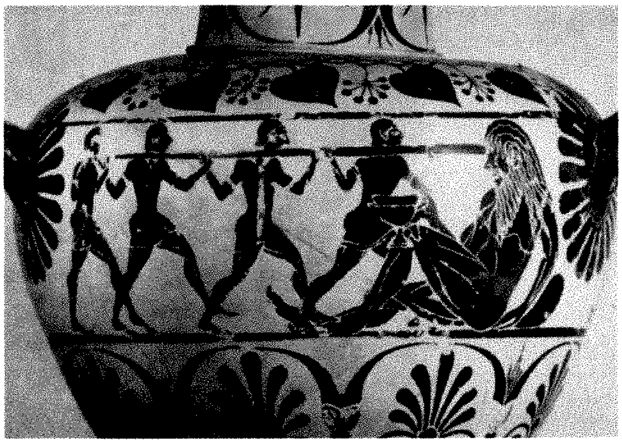

Figure 1. "The Blinding of Polyphemos by Odysseus and his Men." Painting on a hydria from Caere, Etruria, about 520 B.C.; Villa Giulia, Rome. *From left to right*: surgeon (Odysseus), three assistants, anesthesia delivery module (wine tankard), and patient (Polypheme).

parturients in whom the combined spinal-epidural anesthesia was done using the CSEN.

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Ophthalmic Surgery and Vomiting—An Ancient Problem

To the Editor:

Ophthalmic surgery is associated with a high incidence of nausea and vomiting (1). Although this complication is frequently addressed in the anesthetic literature, no reference is made to an early report of vomiting in conjunction with paracentesis/enucleation of an eye ball performed under ethanol anesthesia more than 3000 yr ago (2).

According to Homer's report, Odysseus (and associates) had administered three doses of ethanol to the cyclop Polypheme for the purpose of presurgical sedation. Hypnosis was complicated by emesis of wine and undigested food; aspiration was, despite the supine position, prevented by rotation of the head. Enucleation was performed by direct puncture of the globe, which was followed by severe (probably arterial) bleeding and loss of vitreous humor.

In the English translation by Alexander Pope from 1745, the respective paragraphs read as follows:

I [Odysseus] then approach'd him [Polypheme] reeking with their goar,
And held the brimming goblet foaming o'er:
Cyclop! since human flesh has been thy feast,
Now drain this goblet, potent to digest:
. . .
He heard, he took, and pouring down his throat,
Delighted swill'd the large luxurious draught.
. . .
He said, and greedy grasp'd the heady bowl,
Thrice drain'd, and pour'd the deluge on his foul.
His sense lay cover'd with the dozy fume;
. . .
He said: then nodding with the fumes of wine
Dropped his huge head, and snoring lay supine.
His neck obliquely o'er his shoulder hung,
Prest with the weight of sleep that tames the strong!
There belched the mingled steams of wine and blood
And human flesh, his indigested food.
. . .
Then forth the vengeful instrument I bring;
With beating hearts my fellows form a ring.
Urg'd by some present god, they swift let fall
The pointed torment on his visual ball.
My self above them from a rising ground
Guide the sharp stake, and twirl it round and round.
. . .
The grain deep-piercing till it scoops it out:
In his broad eye so whirls the fiery wood;
From his pierc'd pupil spouts the boiling blood;
Sing'd are his brows; the scorching lids grow black;
The gelly bubbles, and the fibres crack.

Recovery from anesthesia apparently was rapid and uneventful, as indicated by early resumption of coordinated speech:

He sends a dreadful groan: the rocks around
Thro'all their inmost-winding caves resound.
. . .

Then calls the cyclops, all that round him dwell,
With voice like thunder, and a direful yell.

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References

1. Morrison JD, Mirakhur RK, Craig HJL, eds. Anaesthesia for eye, ear, nose and throat surgery. 2nd ed. Edinburgh: Churchill Livingstone, 1985.
2. Pope A. Homer's Odyssey. Book IX. London: H. Lintot, 1745.

Is the Cardiovascular Response to Electroconvulsive Therapy Due to the Electricity or the Subsequent Convulsion?

To the Editor:

We read with interest the article by Partridge et al. (1). The authors suggest "it is not the seizure per se that produces the cardiovascular response [tachycardia, hypertension] to electroconvulsive therapy but rather the electrical stimulus or a combination of the stimulus and the resulting seizure." In support of this premise, the authors present a patient in whom transient hypertension and tachycardia developed in response to a subconvulsive electroconvulsive therapy (ECT) stimulus and no hemodynamic response to a spontaneous generalized convulsion.

A review of the pertinent literature, however, suggests contrary conclusions. First, subconvulsive stimuli have been reported to be associated with transient bradycardia or hypotension (2–4). In practice, a variety of responses to subconvulsive ECT stimuli can be observed, including transient hypertension, hypotension, tachycardia, bradycardia, or sinus pauses. This view is based on our experience with more than 100 patients receiving subconvulsive ECT stimuli in an effort to define their seizure threshold. Second, spontaneous modified generalized seizures typically increase heart rate and blood pressure (5).

Next, Partridge and colleagues speculate that medication-induced convulsions may be associated with less cardiovascular risk, i.e., by avoiding the electrical stimulus. To the contrary, metrazol convulsive therapy produces significant hypertension and tachycardia (5). The authors' suggestion that isoflurane may be useful in treating depression has already been cast in doubt (6).

Furthermore, the authors' recommendation that "if a patient responds to ECT with significant tachycardia or hypertension . . . then it is appropriate to pretreat with a cardioactive agent to blunt this . . . response" is debatable. Controlled studies should be carried out before making sweeping recommendations that go against established practice (7). In this regard, the specific recommendation of esmolol as a pretreatment to limit ECT-related hemodynamic changes without affecting ECT efficacy is also questionable. Others in this journal, for example, have shown that esmolol shortens seizure duration, an important contributor to ECT efficacy (8). We have previously shown that labetalol controls ECT-related hemodynamic changes without affecting seizure duration (9).

In summary, the authors have presented insufficient evidence to support their conclusions that the ECT electrical stimulus, not the seizure, produces tachycardia and hypertension, or that alternative treatments (metrazol, isoflurane) would be safer or more effective.

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References

1. Partridge BL, Weinger MB, Hauger R. Is the cardiovascular response to electroconvulsive therapy due to the electricity or the subsequent convulsion? Anesth Analg 1991;72:706–9.
2. Thompson WA. Subconvulsive electric shock treatment of the psychoses. Am J Psychiatry 1942;99:382–6.
3. Patterson AS, Conachy A. Subconvulsive electrical stimulation in the treatment of chronic neurosis. Br Med J 1952;4795:1170–4.
4. Wells DG, Zelcer J, Treadrae C. ECT-induced asystole from a subconvulsive shock. Anaesth Intensive Care 1988;16:368–73.
5. Mosier JM, White P, Grant P, Fisher JE, Taylor R. Cerebroautonomic and myographic changes accompanying induced seizures. Neurology 1957;7:204–10.
6. Greenberg LB, Gage J, Vitkun S, Fink M. Isoflurane anesthesia therapy: a replacement for ECT in depressive disorders? Convulsive Ther 1987;3:269–77.
7. American Psychiatric Association. The Practice of ECT: recommendations for practice, training and privileging. Task Force Report on ECT. Washington, DC: American Psychiatric Press, 1990.
8. Howie MB, Black HA, Zvara D, McSweeney TD, Martin DJ, Coffman JA. Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. Anesth Analg 1990;71:384–8.
9. McCall WV, Shelp FE, Weiner RD, Austin S, Harril A. Effects of labetalol on hemodynamics and seizure duration during ECT. Convulsive Ther 1991;7:5–14.

In Response:

We appreciate the interest Dr. McCall and colleagues have shown in our recent case report in which we hypothesized that the electrical shock itself might be at least as important as the resultant seizure in producing the cardiovascular responses commonly associated with ECT (1). It was never our intention to suggest that a single case report would *prove* this theory. Rather, we presented this case because it was an unusual clinical event, which suggested an interesting hypothesis that, to our knowledge, had not been previously espoused. McCall et al. take exception to this theory. We welcome the opportunity to comment on a number of points in their letter.

We *do* agree with McCall et al. that a variety of hemodynamic responses may result from "subconvulsive" electric shock treatment. These subconvulsive treatments, in which the patient receives an electrical stimulus that falls short of producing a generalized seizure, have been shown to produce "stimulation of the autonomic nervous system, which in some cases is very pronounced" (2). In both the report by Patterson and Conachy (2) and the earlier one by Thompson (3), a transient sympathetic discharge (with associated hypertension) is described. However, it is true that in some patients, parasympathetic activity may instead be prominent. There appears to be a significant degree of patient variability, which may depend on the underlying balance of sympathetic versus parasympathetic tone.

One must thus be careful in extrapolating the results of individual cases, outdated techniques, or techniques using other anesthetic or pharmacologic interventions to predict the hemodynamic consequences of modern ECT in otherwise healthy patients. In one of the cases cited by McCall et al., Wells and colleagues (4) describe a 75-yr-old patient who had experienced a prior inferior wall myocardial infarction, had poor left ventricular function, and had an electrocardiogram showing both first-degree atrioventricular block and a right bundle branch block. Before ECT, he received both nifedipine (10 mg) and atropine (0.4 mg). Etomidate (12 mg) rather than methohexital was used for anesthetic induction. In light of these predisposing physiologic and pharmacologic factors, it is perhaps not a complete surprise that this patient responded to the ECT stimulus initially with asystole.

We also agree with McCall et al. that currently available convulsant medications may either be without therapeutic benefit (e.g., isoflurance [5]) or produce undesirable hemodynamic changes (e.g., metrizol [6]). However, our statement was only conjectural in nature, and the potential benefits of newer drugs such as RO 15-4513 or the β-carbolines remain to be examined. A close-minded outlook might stifle valuable research on the many new pharmacologic agents under development.

In a recent study, published in this journal, we examined the cardiovascular (7) and neuroendocrine (8) effects of ECT after pretreatment of 10 patients with esmolol (1.0 mg/kg), fentanyl (1.5 μg/kg), labetalol (0.3 mg/kg), lidocaine (1.0 mg/kg), or saline control in a double-blind, randomized block design. Each patient received all five pretreatment regimens over the course of five ECT sessions. During control studies, arterial blood pressure and heart rate increased significantly in all patients after ECT. There were, however, appreciable individual differences in the cardiovascular response to ECT independent of pretreatment. Pretreatment with esmolol and labetalol significantly reduced the hemodynamic response to ECT compared with fentanyl, lidocaine, or saline. Esmolol attenuated blood pressure *to a greater extent* than did labetalol. Compared with saline control, pretreatment with labetalol, fentanyl, or lidocaine significantly reduced seizure duration and increased the frequency with which a second electrical stimulus was required. In contrast, esmolol pretreatment did not significantly affect seizure duration or the requirements for a second electrical stimulus. In addition, pretreatment with esmolol resulted in significant attenuation of catecholamine release after seizure.

Our results are in contrast to those of Howie et al. (9), who used a continuous esmolol infusion resulting in a total esmolol dose of approximately four times higher than we used. With this unnecessarily higher dose, they found a comparable attenuation of blood pressure and heart rate but also reduced seizure duration.

McCall and colleagues (10) very recently reported the results of their study examining the effects on hemodynamics after ECT of two doses of labetalol (5 and 10 mg per patient) which were appreciably smaller than that used in our study (0.3 mg/kg). In contrast to our finding of reduced blood pressure, heart rate, and seizure duration, they showed that the smaller doses of labetalol attenuated the heart rate response but had no effect on the blood pressure response or on seizure duration.

Based on the results of our study, we concluded that esmolol (1 mg/kg) administered 1 min before induction of anesthesia produced significant amelioration of the cardiovascular response to ECT with minimal effect on seizure duration. Such a clinical recommendation, which is based on a well-controlled study, appears to us to be *entirely consistent with* the published recommendations of the American Psychiatric Association Task Force (11).

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References

1. Partridge BL, Weinger MB, Hauger R. Is the cardiovascular response to electroconvulsive therapy due to the electricity or the subsequent convulsion? Anesth Analg 1991;72:706–9.
2. Patterson AS, Conachy A. Subconvulsive electrical stimulation in the treatment of chronic neurosis. Br Med J 1952;2:1170–4.
3. Thompson WA. Subconvulsive electric shock treatment of the psychoses. Am J Psychiatry 1942;99:382–6.
4. Wells DG, Zelcer J, Treadrae C. ECT-induced asystole from a subconvulsive shock. Anaesth Intensive Care 1988;16:368–73.
5. Greenberg LB, Gage J, Vitkun S, Fink M. Isoflurance anesthesia therapy: a replacement for ECT in depressive disorders? Convulsive Ther 1987;3:269–77.
6. Mosler JM, White P, Grant P, Fisher JE, Taylor R. Cerebroautonomic and myographic changes accompanying induced seizures. Neurology 1957;7:204–10.
7. Weinger MB, Partridge BL, Hauger R. Preventing the cardiovascular and neuroendocrine response to electroconvulsive therapy: 1. Effects of pretreatment regimens on hemodynamics. Anesth Analg 1991;73:556–62.
8. Weinger MB, Partridge BL, Hauger R, Mirow A, Brown M. Preventing the cardiovascular and neuroendocrine response to electroconvulsive therapy: 2. Effects of pretreatment regimens on catecholamines, ACTH, vasopressin and cortisol. Anesth Analg 1991;73:563–9.
9. Howie MB, Black HA, Zvara D, McSweeney TD, Martin DJ, Coffman JA. Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. Anesth Analg 1990;71:384–8.
10. McCall WV, Shelp FE, Weiner RD, Austin S, Harrill A. Effects of labetalol on hemodynamics and seizure duration during ECT. Convulsive Ther 1991;7:5–14.
11. Weiner RD, Fink M, Hammersley DW, Small IF, Moench LA, Sackheim H. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging. Report of the American Psychiatric Association Task Force on Electroconvulsive Therapy. Washington, D.C.: American Psychiatric Association 1990.

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Norig Ellison

Book Reviews

Critical Issues in Critical Care

Volume 9, No. 2 of Anesthesiology Clinics of North America

Vladimir Kvetan and T. James Gallagher, eds.
Philadelphia: W.B. Saunders, 1991, 255 pp, $32.00 (single issue), $74.00 (per year in U.S. as individual subscriber).

This issue of the Anesthesiology Clinics focuses on current critical issues in critical care and can be recommended as a good source for current reviews in the field. It is particularly timely as the use of scarce and expensive resources in health care in the United States is under increasing scrutiny, driven by the fiscal challenges of existing DRG-payment schemes to hospitals, by the proposed RBRVS schemes for payments to doctors based on work by Hsiao and others from Harvard, and by an economic recession. The ethics and language of allocation of resources are carefully examined and well explained in two of the contributions. These will repay careful study by all practitioners in the field.

The guest editors, Drs. Kvetan and Gallagher, have assembled 14 chapters from 31 authors not only from New York and Florida, their home states, but also from Montreal and Baltimore. These contributions cover a broad range of topics relevant to current management of critically ill patients. The first three chapters provide classical reviews of pathophysiology and pharmacology covering monitoring and management of respiratory failure, oxygenation and blood flow and vasodilating drugs, and regional circulation focusing on the pulmonary vasculature. This third contribution by Bjorn Skeie and colleagues is most informative.

The next two contributions review supportive care modalities. The first focuses on extracorporeal methods from hemodialysis through plasmapheresis to Gattinoni's techniques (JAMA 1986;256:881) referencing the recent and current prospective trial of this ECCO$_2$R (extracorporeal carbon dioxide removal) and LFPPV (low-frequency positive pressure ventilation) technique, coordinated by Morris and colleagues from Salt Lake City, Utah (Trans Am Soc Artif Intern Organs 1988;11:48). Although broad-brushed, this is in fact a very useful review. The second contribution in this section from Askanazi's group gives an excellent review of metabolic support and its rationale. This chapter alone is worth the price of admission.

The next seven chapters focus on major clinical syndromes and deal in turn with the immunocompromised patient, hepatic and cardiac transplantation, drug overdose in 1990 New York style, brain injury, the high-risk cardiac patient for vascular surgery, gastrointestinal crises, and finally trauma. The review of gastrointestinal crises in the ICU is a very timely review of those conditions that are now fairly commonly seen as complications of prolonged ICU care. There has been a changing spectrum of disease that has moved beyond the early concentration on gastrointestinal hemorrhage as the main entity recognized. The contribution on trauma from the Maryland Institute of Emergency Medicine builds on the strong base of experience provided there since the early 1970s when Crawford McAslan, now deceased, working with Shin and Mackenzie pioneered an anesthesiology component in trauma management from the roadside to the ICU. The final two chapters, as already mentioned, deal with ethics and allocation.

One can recommend the whole of this volume as a "must read" for any anesthesiologist currently interested in intensive care and to all candidates and examiners for the ABA certificate of special competence in critical care. In addition, this work should be of interest to others in critical care medicine. The timeliness and strengths of several of the reviews will keep this volume in use and off library shelves for several years to come.

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Recovery From Anesthesia

Volume 29, No. 2 of the International Anesthesiology Clinics

P. W. Lebowitz, ed. Boston: Little Brown & Company, 1991, 121 pp, $81.00.

With a rapidly expanding body of anesthesia literature, anesthesiologists are constantly forced to choose between books that examine similar topics. The selection often comes down to whether the reader is willing to partake of a "snack" or a "meal." *Recovery From Anesthesia* is a concise, well-edited monograph that certainly falls within the former category.

Composed of nine chapters covering topics from hemodynamic instability and respiratory complications to pharmacologic antagonists, the text reads smoothly and remains uniform throughout its varied authorship. Several chapters provide only a cursory examination of their subject, in particular the areas of emergence hemodynamics and recovery of psychologic function after anesthesia. These are offset by solid chapters on the recovery of children, complications during recovery, and an in-depth look at the emerging body of work dealing with benzodiazepine antagonists, most notably flumazenil.

Recovery From Anesthesia provides a quick, enjoyable overview of frequent problems encountered in the postanesthesia care unit and provides an excellent companion text for a rotating anesthesia resident. The book also provides the practicing anesthesiologist a refreshing new outlook on

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an area of our practice that is often downplayed. As the editor points out in his preface, the recovery period is often an anesthetic "Miller time," when vigilance is lowered and we often start thinking about "lighter concerns or our next case." With the guidance of this monograph the concept of emergence as a "destabilizing influence on homeostasis" will gain wider acceptance.

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Pain and Post Anesthesia Management
Volume 3, No. 1 of Critical Care Nursing Clinics of North America

K. Litwack, ed. Philadelphia: W.B. Saunders, 1991, 164 pp, $22.00 for single issue, $49.00 (annual subscription for four issues).

The explosion of medical literature for anesthesiologists has been accompanied by a similar phenomenon in PACU nursing. This volume in the *Critical Care Nursing Clinics of North America* is an example. Nineteen of the 29 authors are registered nurses, and the 18 chapters present a nursing perspective on pain and postanesthesia management.

Nine of the chapters concern the problem of perioperative pain management. The opening chapter covers the concept of pain and its historical development but is necessarily not specific to PACU management. The second chapter describes the clinical assessment of pain but is more specific to the critical care nursing environment. The following chapter outlines the pharmacologic armamentarium for pain treatment but regrettably devotes only two sentences to ketorolac (Toradol, the new injectable nonsteroidal antiinflammatory agent likely to see increasing use in the PACU). Two excellent chapters concerning postoperative epidural analgesia and patient-controlled analgesia for postoperative pain are then presented. An additional two chapters concern regional anesthetic techniques and pediatric pain management. The latter discussion is particularly insightful clinically but fails to mention the popular technique of caudal analgesia in pediatric anesthesia and surgery. The final two pain management chapters concern differential diagnosis of chest pain and nonpharmacologic methods (e.g., TENS, acupuncture, biofeedback) of pain therapy.

The second half of the volume covers a diverse range of topics. Included are two thorough and clinically salient discussions of postoperative pulmonary dysfunction and hemodynamic monitoring. An outline discussion of arrhythmias in the PACU follows. An orphaned topic appears to be the assessment of postoperative 12-lead ECG changes and their management. Discussions of fluid therapy and coagulopathy are presented, followed by a review of malignant hyperthermia. The most compelling chapter in the volume concerns the problem of hypothermia in the PACU and appropriately indicts physicians in the operating room for this preventable morbidity. Two chapters concerning emergence delirium and neuromuscular blocking drugs conclude the volume.

Overall the chapters give a thorough discussion of each topic. Some omissions include the topics of PACU issues in ambulatory anesthesia, postoperative hypertension, and, surprisingly, the ubiquitous problem of nausea and vomiting.

In summary, this is a volume on pain and postanesthesia management written mostly by nurses for nurses. It may find utility for anesthesiologists as an educational tool for PACU nurses, with caveats as above. For the interested reader, it also provides insight on current educational priorities and perspectives used by nursing educators for the PACU.

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Manual of Pain Management

Carol A. Warfield, ed., Philadelphia: J. B. Lippincott, 1991, 384 pp, $49.50.

This manual is edited by the director of the pain management center at Beth Israel Hospital. She has recruited as contributors experts from most fields involved with pain management, for the most part from people around Boston but with some outside personnel. The scope of the book includes acute pain, chronic benign pain, and cancer pain and is broken down into sections on understanding pain, pain by anatomic location, common painful syndromes, and pain management. There are 67 chapters, each approximately 3–5 pages long.

As is frequently the case with a large number of authors and one central editor, the information is not necessarily well-integrated, is frequently repetitive, and does contain significant inconsistencies. Nonetheless, many of these chapters are well-written vignettes on specific pain problems. The greatest weakness of this book is that, in general, it really gives no concept of interdisciplinary pain management. The chapters reveal disciplines of techniques, acting to some extent in a void and not interrelating with other disciplines. This is particularly noted in issues regarding physical therapy where, in sections like the myofascial pain chapter, there is no mention of a prolonged exercise regimen. This also would include behavioral medicine in chapters written by physicians.

In the first section on understanding pain, the first three chapters are not integrated and are somewhat repetitive. The chapter on psychologic factors is somewhat one-sided and oversimplified, leading the reader to believe that pain is either all somatic or all psychologic rather than the usual mixture of both somatic pain problems and psychologic features that help prolong the pain. The chapter on diagnostic measurements is only a discussion on diagnostic blocks and does not mention EMGs, SSEPs, MRIs, or other studies that can help give diagnostic information. There are no statements regarding failed blocks or how inappropriate use of somatic blocks can provide inappropriate information. In discussing situations where peripheral neural blockade does not relieve pain, statements are made that the pain is, therefore, psychogenic rather than central. This demonstrates some bias that is not well founded. There are nonpsychogenics that can cause pain to remain when peripheral blockade is performed. The section on pain by anatomic location seems incomplete as well. For instance, the chapter on pelvic pain does not mention any skeletal or myofascial sources, and the pain of the extremities is limited to neuralgias with no mention of other structures or of pain sources.

Overall, I would not recommend this book as a manual of pain management, either for complete information of the more common pain syndromes or for an interdisciplinary approach toward pain, which has been a major part of the focus for pain management over the last several years.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Aldrete JA, ed. *Texto de Anestesiologia Teorico-Practica,* Mexico City: Salvat Mexicana de Ediciones, 1991, 1838 pages (2 volumes), $63.00.

Morris DB. *The Culture of Pain.* Los Angeles: University of California Press, 1991, 375 pages, $29.95.

Notice

ASA Members:

The ASA Task Force on Practice Parameters—Pulmonary Artery Catheterization Monitoring is seeking input from the ASA membership into the writing of Guidelines for Pulmonary Artery Catheterization Monitoring. To help the Task Force assure that it has access to all relevant information on the indications for and value of pulmonary artery catheterization, members of the Task Force would appreciate your sending them references to scientific articles or to other published information that you have found helpful in guiding your use of pulmonary artery monitoring. Furthermore, an open forum will be held to discuss the guideline and its draft development on March 15, 1992 from 2 to 5 PM at the IARS Meeting in San Francisco. You will have ample opportunity to review the guidelines before that and to comment on and have input into the guidelines by talking to members of the Task Force. The Task Force is also interested in reviewing draft articles, abstracts, or other information on pulmonary artery catheterization and its monitoring that have not been published. Please send your lists of references, articles, or copies of unpublished documents to: Michael F. Roizen, MD, Chairman, ASA Task Force on Practice Parameters—Pulmonary Artery Catheterization Monitoring, Department of Anesthesia and Critical Care, The University of Chicago, 5841 South Maryland Avenue, Box 428, Chicago, IL 60637. FAX: (312) 702-3535.

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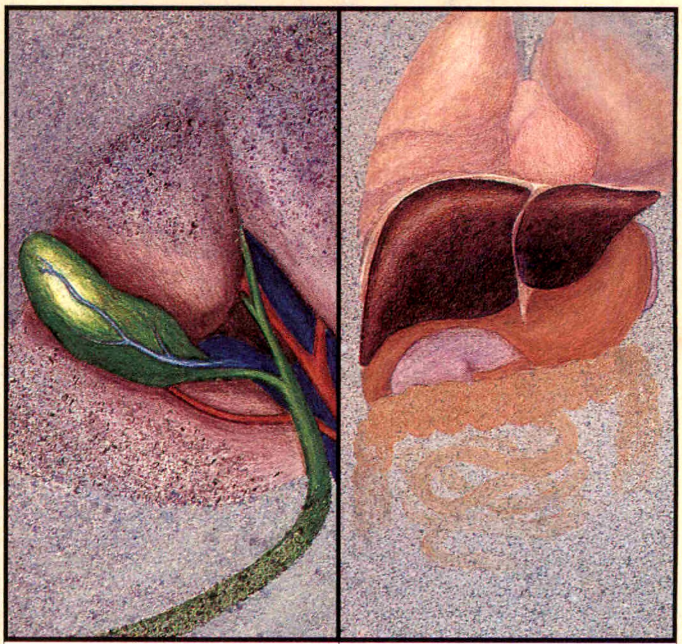

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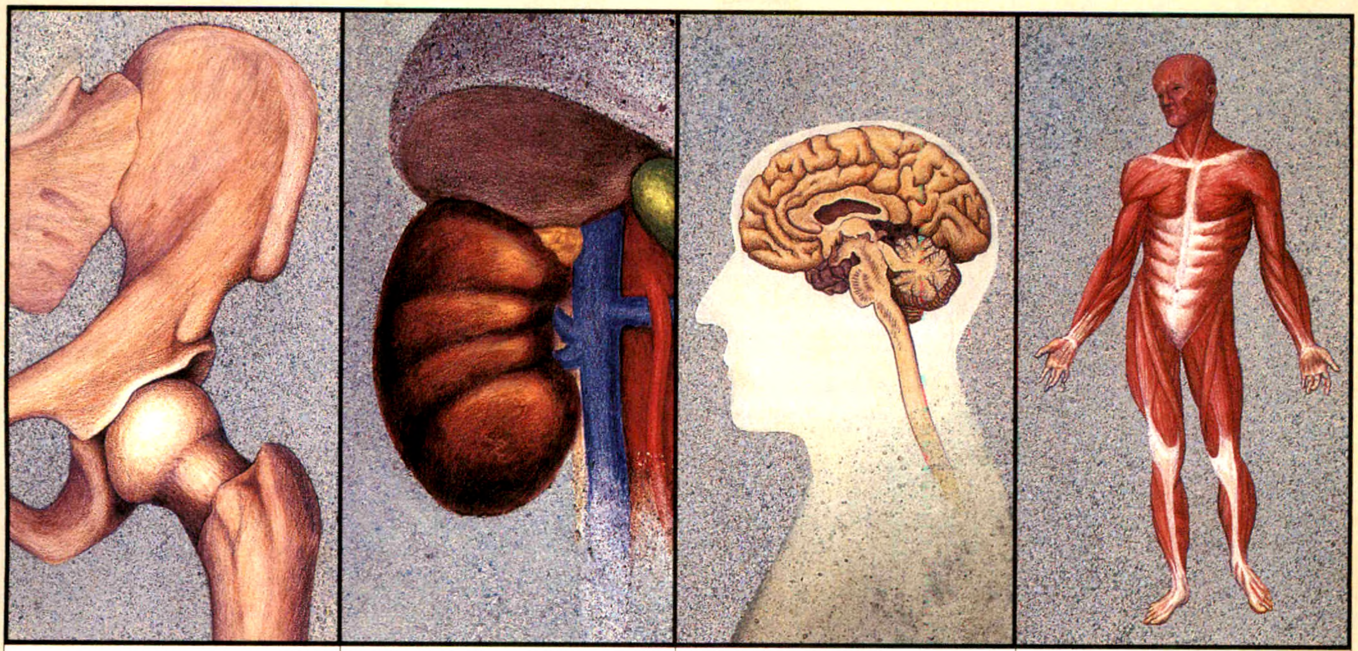

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INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

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WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy: *Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use Tracrium Injection within 14 days even if rerefrigerated.

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1. Weinstein JA, Matteo RS, Ornstein E, Schwartz A, Goldstoff M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg.* 1988;67:1149-1153. **2.** Ward S, Neill EAM. Pharmacokinetics of atracurium in patients in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172. **3.** d'Hollander A, Luyckx C, Barvais L, DeVille A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology.* 1983;59:237-240. **4.** Ornstein E, Matteo RS, Silverberg PA, Schwartz AE, Young WL, Diaz J. Chronic phenytoin therapy and nondepolarizing muscular blockade. *Anesthesiology.* 1985;63:A331. Abstract. **5.** Ebrahim Z, Bulkey R, Roth S. Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg.* 1988;67:S55. Abstract.

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San Francisco, California
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Abstracts:	S1–S368
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Journal of the International Anesthesia Research Society

S1

QUANTITATIVE ASSESSMENT OF SEVERE PAIN USING NONINVASIVE SURFACE ELECTROMYOGRAPHY

W Ackerman, MD, H Edmonds, PhD, V Cases Cristobal, MD, M Juneja, MD, K Belinger, Ed.D., S Tabatabae, BS, B Rigor, MD
Department of Anesthesiology, University of Louisville, School of Medicine, Louisville, KY 40292

Difficulty exists quantifying severe pain. Visual and verbal analogue pain scores are subjective representations of pain. The efficacy of EMG monitoring to assess the depths of anesthesia during general anesthesia has been demonstrated.[1] This study assessed the efficacy of noninvasive quantitative surface electromyography (QSEMG) in quantifying severe pain in awake patients.

Following IRB approval, informed consent was obtained from 12 ASA I or II, G_1,P^0 labor patients who requested epidural analgesia. An Anesthesia and Brain Activity Monitor (ABM) (Datex, Helsinki, Finland) was used for QSEMG analysis. Surface electrode impulses were preamplified to obtain spontaneous EMG signals in a range of 0-100 mcV. Each patient reported a verbal assessment pain score (VAS 0=no pain, 10=worst pain) prior to epidural placement and every 5 min until VAS=0. Following a 2% lidocaine test dose, epidural catheter dosing was done with 0.5% bupivacaine with 2.5 mcg sufentanil/ml. The mean QSEMG amplitude was noted prior to epidural placement during a uterine contraction when each patient reported maximum pain. The QSEMG subsequently was noted during a uterine contraction when the VAS=0. The digitized values were stored in comma-delimited ASCII (LOTUS 1-2-3) files.

Twelve patients were studied. Each patient had a VAS=10 prior to epidural dosing. With severe pain the mean QSEMG amplitude was 11.6 (range 9.2-14.1) mcV with a coefficient of variation =23%. With complete anesthesia the mean QSEMG amplitude was 3.5 (range 2.7-4.3) mcV with a coefficient of variation = 26%. The mean QSEMG decrease was statistically significant (paired two-tailed Student's t-test = 10.4, $p<0.001$) when the severe pain mean amplitude was compared to the VAS=0 mean amplitude.

The QSEMG was effective in quantifying severe acute pain. This investigation was a pilot study to determine if pain could be quantified by QSEMG. As a result, ongoing QSEMG research is being conducted in the ICU and PACU using data from this study to determine the efficacy of QSEMG in the pharmacologic analgesic management of patients unable to verbalize pain intensity.

References

1. Edmonds HL Jr, Paloheimo M. Int J Clin Monit Comput 1:201-210, 1985.

S2

Title: ALTERATIONS OF SUBARACHNOID ANESTHETIC SOLUTIONS FOLLOWING THE ADDITION OF FENTANYL AND MORPHINE.

Authors: GH Adkisson MD, JH Waters MD, GA Burger MD
Affiliation: Naval Hospital, San Diego, CA

Introduction: The addition of small amounts of narcotics to subarachnoid anesthetic solutions has become an accepted option for performing subarachnoid anesthesia. Volume, concentration and baricity may influence the level of anesthesia achieved by a particular solution and the addition of even small quantities of additional medications may change each of these factors. This study determines the density of a measured quantity of commonly administered subarachnoid anesthetic solutions and then calculates the change in volume, concentration and baricity following the addition of fentanyl (F) and morphine (M).

Methods: Three commonly administered local anesthetic solutions were measured (1.5ml) via micropipette and weighed on a scientific balance accurate to four decimals. The density of each solution was determined. F (25-50ug) or M (.25-.5mg) was added to each solution and the change in density was determined. Changes in volume and concentration of each solution were calculated and baricity was determined using 1.0003 as a baseline for cerebrospinal fluid (CSF). All measurements were at 22°C.

Results: Changes in density and baricity are tabulated below.

DRUG	BAR	F25	F50	M25	M50
L5G	1.0017	.9898	.9838	.9921	.9853
T.5	1.0331	1.0270	1.0208	1.0266	1.022
B.75	.9951	.9895	.9835	.9886	.9841

F25=25ug, F50=50ug, M25=.25mg, M50=.50mg
BAR=Baricity, L5G=Lidocaine 5% in glucose, T.5=Tetracaine .5% in glucose, B.75 = Bupivicaine .75% in glucose

Hyperbaric solutions may become isobaric or even hypobaric in some cases. Volume increases and concentration decreases along with these changes in baricity.

Discussion: Altering anesthetic solutions has potential clinical importance. While numerous other factors have been implicated in the spread of subarachnoid anesthetics, unplanned changes in volume, concentration and baricity may result in an altered blockade.

S3

TITLE: COMPARISON OF α_2-AGONIST, DEXMEDETOMIDINE AND MIDAZOLAM AND ANTAGONISM OF DEXMEDETOMIDINE WITH ATIPAMEZOLE

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Introduction: Patients undergoing ambulatory surgery desire a rapid recovery in order to resume their normal activities. The selective α_2-agonist, dexmedetomidine (dex) has sedative effects.[1] It attenuates the hemodynamic response to laryngoscopy and intubation and decreases the isoflurane requirements during abdominal hysterectomy.[2] Atipamezole is a selective α_2-adrenoceptor antagonist, which in humans effectively reverses the sedative, sympatholytic and cardiovascular effects of dex.[3] The present study evaluated the use of dex as an intravenous sedative agent and the effect of atipamezole on recovery in patients undergoing cervical dilatation and currettage of uterus.

Methods: This double-blind study was approved by the Ethical Committee of the Hospital and comprised 72 consenting healthy women, randomly allocated to three groups of 24 patients. An intravaginal prostaglandin was inserted for cervical softening to all patients and meperidine 1.0 $mg.kg^{-1}$ i.m. was administered as premedication. Prior to the administration of the sedative study drug every patient received glycopyrrolate 0.2 mg. Dex 2.0$\mu g.kg^{-1}$ or midazolam 0.15$mg.kg^{-1}$ i.v. were administered as the first study drug (I) three minutes before paracervical blockade with lidocaine. Alfentanil 15$\mu g.kg^{-1}$ i.v. was administered, when performing the paracervical blockade. The cervical dilatation did not begin sooner than 3 min after performing the blockade. During the operation patients received 30% oxygen in nitrous oxide using spontaneous or assisted ventilation. If the effect of paracervical blockade and study drug was unsatisfactory (patient was moving making it difficult to continue the procedure), propofol was administered in 0.5$mg.kg^{-1}$ i.v. incremental doses. At the end of the operation the patients received the reversal study drug: dex-treated patients received either saline or atipamezole 0.05$mg.kg^{-1}$ i.v.
The patients assessed sedation with a Visual Analog Scale (VAS), and impairment of vigilance with the Maddox Wing apparatus 10, 30, 60 and 120 minutes after the reversal agent. Digit Symbol Substitution Test (DSST) was performed 30, 60 and 120 min after the reversal agent. ANOVA for repeated measurements, followed by Bonferroni corrected t-test for pairwise comparisons in different time points, was used for statistical analysis; propofol requirements were analyzed with the Chi-square test.

Results: The main results are shown in Table (mean±SD). Dex (23%) treated patients required more supplemental propofol than the midazolam group (4%) (p<0.05). Dex initially increased blood pressure and decreased heart rate during the first minutes after administration of the drugs. In the recovery room patients who had received saline after dex had lower heart rate than the dex group which received atipamezole as reversal agent or who were treated with midazolam. The mean time to regain consciousness was significantly longer in the midazolam group. During the recovery period, atipamezole-treated patients were least sedated as assessed with VAS and the Maddox Wing, and also they performed best in the DSST.

Discussion: Intravenous dex was less sedative than midazolam and dex treated patients required more supplemental doses of propofol. Midazolam caused adequate, but undesirably long-lasting sedation for the procedure. Reversing dexmedetomidine sedation with atipamezole improved the recuperation from anesthesia. Higher intravenous dex doses induced a significant initial increase in blood pressure.

Sedative drug: Reversal drug:		Midazolam Saline	Dex Saline	Dex Atipamezole
No of patients		24	24	24
MAP after study drug I (mmHg)		84±10	96±7**	98±14***
HR after study drug I (bpm)		79±15	53±10***	58±11***
Response to verbal command (min)		8.1±7.7	1.7+2.5***	1.6±1.3***
Sedation VAS (cm)	10 min	7.8±2.7	8.7±1.3	5.9±2.7*
	30 min	7.3±2.2	7.0±1.8	5.4±2.4*
	60 min	6.2±2.4	5.5±2.1	4.6±2.4
	120 min	3.8±2.9	3.0±2.4	4.0±2.7
Maddox Wing (diopters)	10 min	13±5	11±6	4±5***
	30 min	12±5	8±6*	4±5***
	60 min	10±4	8±7	4±5***
	120 min	8±5	4±4**	4±5**
DSST (# correct)	30 min	25±19	38±21	59±18***
	60 min	36±23	47±22	62±21***
	120 min	51±21	68±22	61±21

*p<0.05, **p<0.01
***p<0.001 vs midazolam

References:
1. Br J Clin Pharmacol 24:443-451,1987
2. Anesth Analg (Suppl) 70:S5,1990
3. Br J Clin Pharmacol 31:160-165, 1991

S4

Title: THE PERFORMANCE OF A DRAW-OVER VAPORIZER AND ITS ANESTHETIC CIRCUITRY IN THE LABORATORY

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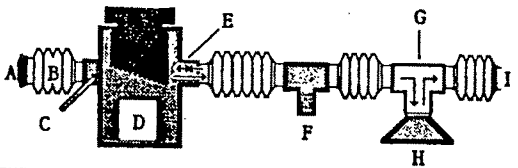
Introduction: Operating circumstances frequently posed during military conflicts and natural disasters mitigate that U.S. anesthesiologists must be acquainted with contingency anesthetic delivery systems and consider their advantages and limitations. In this study, we assess the output performance of a new thermo-compensated Ohmeda Cyprane PAC draw-over vaporizer using isoflurane attached to a non-rebreathing circuit under simulated adverse conditions.

Methods: The output (%) of the vaporizer was measured at position "H" (Fig I) in adult and pediatric ventilation modes of minute volumes of 750 ml x 12 and 150 ml x 30, using a self-inflating bag at 20°C. In simulation of adverse circumstances which may be expected to occur in the "field," vaporizer output was also measured: a) at 39°C; b) in 90° lateral tilt; c) in 90° anterior tilt; d) in 180° full inversion; and e) during continuous agitation with orientation varying randomly through 0° - 90° in all directions. Vaporizer and circuit function were also evaluated with a Penlon Oxford compressed air-driven ventilator.

Results: With the vaporizer upright at 20° ambient temperature, isoflurane output matched the set dial concentrations. Tilting, overturning, agitating, and increasing the ambient temperature of the vaporizer consistently resulted in output concentrations in excess of the indicated settings when tested at 1, 2, and 3%. These changes were clinically significant, asthey ranged beyond the accepted ±0.5% error bounds. No vapor was detected at any vaporizer setting when the Penlon ventilator was attached at position "F", which is contrary to previous reports. The reason for this observation is that the Penlon is unable to "draw" any vapor from the vaporizer.

Conclusion: Varying the orientation and temperature of the PAC vaporizer did not significantly affect its performance at settings of 0.5, 4, or 5%. At other settings, output was consistently higher than indicated. When this vaporizer and the non-rebreathing circuit are used with controlled ventilation, it is essential to utilize a self-inflating apparatus or a pump-type ventilator (e.g. the Palmer Starling Ideal pump) in order to ensure delivery of anesthetic gases. These findings represent new and clinically relevant information regarding the use of this valuable anesthesia delivery system.



LEGEND
A. Air Inlet w/dust filter
B. Oxygen Economizer Tube
C. Supplementary Oxygen Inlet
D. PAC Vaporizer
E. Vaporizer Outlet Port
F. Controlled Vent. Port
G. One-Way Valve
H. Pt Airway Access Port
I. Waste Gas Exhaust (to scavenger)

S5

Title: POSTOPERATIVE ANALGESIA: EPIDURAL FENTANYL VS. IV PCA MORPHINE

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Introduction: Both patient-controlled intravenous infusions (PCA) and epidural infusions of narcotics are used for postoperative analgesia at our medical center. This IRB-approved prospective study compared the effectiveness of these two analgesic regimens in 66 men undergoing bilateral pelvic lymph node dissection with radical retropubic prostatectomy.

Methods: Following informed consent and the anesthesiologist's decision regarding general or epidural anesthesia, patients were randomized to receive either PCA i.v. morphine (Group P, n=33) or epidural fentanyl (Group E, n=33) for postoperative analgesia. Patients were instructed in the 0-10 VAS scale for assessment of pain at rest and the 0-10 verbal response scale for assessment of pain with deep breathing, coughing and ambulating. Other parameters monitored included side effects (nausea, vomiting, pruritus, respiratory depression), bladder spasm, ABG, SaO_2, Hgb, Na+, Cr, and duration of hospital stay. Patients in both groups were evaluated while awake by a trained observer at 1600 h and 2000 h on the day of surgery (DOS) and at 0800 h, 1200 h, 1600 h, and 2000 h daily until 0800 h on postoperative day 3 (POD 3). The rank sum test was used for statistical analysis of VAS data. A two-tail $p \leq 0.05$ was significant.

Results: No statistically significant intergroup differences were found in biophysical profiles, frequency of side effects, laboratory values, or duration of hospital stay. Choice of anesthetic had no significant impact on postoperative analgesia. Mean resting pain scores were lower in Group E at all 11 observation times, with statistical significance at 9 times (Table). Maximum pain scores were significantly lower in Group E (Table).

Discussion: When two effective methods for postoperative analgesia were compared prospectively, patients receiving epidural fentanyl were more comfortable.

Resting Pain Score,* Mean (± SD)				
Day	Time (h)	Group E	Group P	P
DOS	1600	1.96 ± 1.79	5.01 ± 2.39	0.002
	2000	2.01 ± 1.94	3.25 ± 1.65	0.008
POD1	0800	1.73 ± 1.86	3.27 ± 1.91	0.003
	1200	1.70 ± 1.97	2.71 ± 1.64	0.020
	1600	1.23 ± 1.52	2.53 ± 1.80	0.002
	2000	1.47 ± 2.13	2.03 ± 1.50	0.034
POD2	0800	0.75 ± 1.05	2.11 ± 1.67	<0.001
	1200	0.60 ± 0.83	1.57 ± 0.99	0.001
	1600	0.99 ± 1.85	1.98 ± 1.65	0.008
	2000	1.63 ± 2.75	1.90 ± 1.94	NS
POD3	0800	0.87 ± 1.09	1.30 ± 1.18	NS
Maximum Pain Score, (Mean ± SD)				
Resting*		3.79 (± 2.40)	4.85 ± (1.76)	0.0270
Deep Breathing**		3.64 (± 2.37)	4.82 (± 1.99)	0.043
Cough**		6.23 (± 2.44)	8.03 (± 1.28)	0.002
Ambulate**		4.38 (± 2.61)	5.59 (± 1.61)	0.032

* VAS (Visual Analogue Scale) ** Verbal 0-10 scale

S6

TITLE: EVALUATION OF NONINVASIVE PACING IN THE LATERAL DECUBITUS POSITION AND DURING ONE-LUNG VENTILATION

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Emergency pacing may be required during surgery in the lateral decubitus position (lung, esophagus, orthopedic etc.). Initiation of noninvasive pacing may be faster and safer than temporary transvenous pacing.[1] Data on noninvasive pacing in the lateral decubitus position are sparse. We determined the feasibility, hemodynamic and echocardiographic effects of noninvasive transcutaneous pacing (NTP) in patients having surgery in the lateral decubitus position and one-lung ventilation.

METHODS: With IRB approval and written consents 10 patients without cardiac disease having elective thoracic surgery were studied. All patients were given a thiopental/fentanyl induction and maintained with $0_2/N_20$/isoflurane and vecuronium. Patients were monitored with an arterial line and 2D-transesophageal echocardiography (Hewlett-Packard Sonos 1000). Following stable hemodynamics, patients were paced with the Zoll 1000 at 15-20 beats above their resting heart rate for 60 sec at the following times: 1) Baseline supine 2) Pre-op lateral decubitus 3) One-lung ventilation 4) Post-op lateral decubitus 5) Post-op supine. At each time point blood pressures before and during pacing and the threshold required to achieve pacing capture were recorded as well as echocardiography.

RESULTS: Six patients had a right thoracotomy and four had a left. Pacing capture was achieved in all patients. The pacing threshold required was 95.6 ± 6.4 mA (mean ± S.D., range 55-140). The set paced rate needed to be at least 20 beats per min higher than the desired pacing rate. During pacing all patients showed a decrease in MAP of 16.5 ± 3.8% (mean ± S.D. range 5-34) from baseline (pre-pacing) MAP of 82.76 ± 12.7 mmHg. Decrements in MAP were seen only during pacing and returned to baseline MAP with cessation of pacing. Loss of atrial contraction and paradoxical interventricular septal wall motion were seen by transesophageal echocardiography.

CONCLUSIONS: 1) NTP was effective and without complications in patients undergoing thoracic surgery. 2) In contrast to a previous report,[2] significant decrements in MAP were seen during pacing and most likely are due to the loss of AV-synchrony. 3) Paradoxical septal wall motion, seen in our patients by transesophageal echocardiography, was not appreciated previously.[3]

REFERENCES:

1) Mayo Clinic Proc 1983;58:122. 2) Am J Med 1988;84:395. 3) PACE 1988;11:1188.

S7

TITLE: Does Prophylactic Epidural Blood Patch or Prophylactic Normal Saline Patch Through an Existing Epidural Catheter (EC) Increase the Risk of Infection?

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Introduction: Epidural blood patch and normal saline patch through a pre-existing EC are gaining popularity as a potential prophylaxis against Post Dural Puncture Headache. The latest studies by Ackerman et al[1] and Colonna-Romano et al[2] have noted favorable results. However, colonization at various sites of previously *in situ* ECs by multiple organisms has been reported in surgical and obstetric patients.[3,4] Injecting blood or normal saline through a potentially colonized EC raises the question of increased risk of infection. This study was designed to address this concern.

Methods: After IRB approval, post-partum patients in whom epidural anesthesia/analgesia was delivered were recruited and given informed written consent. Patients were randomized into 2 study groups, Normal Saline (NS) and Autologous Blood (B). In both groups the skin and exposed catheter were rendered sterile using 70% alcohol prep, allowed to air dry,then removed under strict sterile technique. Either normal saline (30ml) or autologous blood (approx. 17ml) was infused through the removed EC with the distal 2-3cm of the EC immersed in the pool of collecting INJECTATE in a sterile urine cup. The EC was then removed from the cup - the distal 3 cm removed and cultured (Maki Technique). 0.1ml of INJECTATE was immediately cultured (TIME ZERO) on a blood agar plate and incubated for 48 hours at 37° C. The remaining INJECTATE was also incubated in its sterile cup for 48 hours at 37° C. At TIME 48 HRS, another 0.1ml was cultured on a new blood agar plate and incubated for another 48 hrs at 37° C. [NOTE: Injectate blood was allowed to clot. At TIME 48 HRS the clotted blood was reliquified with a stomacher and then culture sample taken.] Data collection consisted of quantitative colony counts of INJECTATE at TIME ZERO and TIME 48 HRS. These cultures were sensitive to 10 CFU/ml of INJECTATE. EC tips were semiquantitatively cultured. All positive cultures were subcultured for organism ID. Comparisons were made between the culture growths of Groups NS and B as to the incidences of positive cultures and organisms identified. Statistical analysis of quantitative data was analyzed using unpaired t-test. Statistical analysis of qualitative data was done using X^2. Statistical significance is $p<0.05$.

Results: The maternal characteristics were similar between groups. Three of 12 (25%) "NS" TIME ZERO injectate cultures were positive compared to none in "B" at TIME ZERO. This difference was statistically significant. However at TIME 48 HRS there was no growth in either INJECTATE group. Five of 12 (42%) "NS" EC tips were positive, compared to 3 of 8 (38%) for group "B". This was not statistically significant. ID of organisms revealed only common skin flora.

CULTURE RESULTS

GROUP	Catheter Tips (+)	Injectate (+)	
		Time Zero	48 Hours
Blood (B) N=8	3 (38%)	None	None
Normal(NS) N=12	5 (42%)	3 (25%)	None

Discussion: Though EC colonization does occur, prophylactic patches (using NS or blood) through existing ECs appears not to promote growth, as evidenced by no growth at 48 hrs in either group. Therefore there is no apparent increased risk of infection with this technique.

References: (1.) Anesth Analg 68:51, 1989, (2.) Anesth Analg 69: 522-523, (3.) Anesthesiology 46: 351-354, 1977, (4.) Anesth Analg 56:222-225, 1977

S8

Title: CARDIOPULMONARY EFFECTS OF LAPAROSCOPIC CHOLECYSTECTOMY

Authors: H. Andel, M.D., V. Grabner, M.D., E. Zadrobilek, M.D., T. Twrdy, M.D., K. Leitner, M.D. F.X. Lackner, M.D.
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Introduction: Laparoscopic techniques are thought to be less invasive with the benefit of faster recovery [1]. However, CO2 insufflation into the abdominal cavity may compromise cardiac and pulmonary function [2]. Aim of the study was to quantify these alterations by the use of trans-esophageal echocardiography.

Methods: Fifteen patients (10 female, 5 male), ASA I and II, median age 55 years, median weight 85 kg, consenting to the protocol approved by the hospital ethics committee, were investigated.
Monitoring included heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), end-tidal CO2 tension (PetCO2) and mean airway pressure (mPaw). Stroke volume (SV) and cardiac output (CO) was determined by measuring the mitral valve flow velocity with a pulsed-wave Doppler. Total intravenous anesthesia was performed with propofol-bypass, fentanyl and vecuronium. Tidal volume (TV) was adjusted to maintain PetCO2 between 35 and 40 mm Hg, FIO2 (0.4), respiratory rate (10/min), ratio (1:1) and positive end-expiratory pressure (5 mmHg) were kept constant. Statistical evaluation was performed using Wilcoxon and Student T-test.

Results: In comparison to preinsufflation values (A) a reduction of SV and CO was found intraoperatively (B) whereas blood gas could be kept stable by increasing TV only (table 1).

Discussion: Elevated TV for compensation of CO2 absorption and the increase of mPaw led to a significant, but tolerable decrease in SV and CO. As CVP and MAP rose we suggest that total peripheral resistance increased. Further studies will be necessary before recommending this surgical technique for patients with impaired cardiac function.

Table 1: EFFECTS OF CO2 INSUFFLATION (mean ± SD)

	A	B
HR(b/min)	65±10	71±6*
SV(ml)	73±14	57±15**
CO(l/min)	4.7±0.6	4.1±0.7*
MAP(mm Hg)	83±12	101±16**
CVP(mmHg)	12±3	15±4*
mPaw(mm Hg)	13±2	15±3**
paO2(mmHg)	134±21	138±11

*: $p < 0.05$ and **: $p < 0.01$ compared to A

References: 1.Anesthesiology 73:1268-1270, 1990
2.Acta Anaesth Scand 33:132-136, 1989

S9

Title: EPIDURAL VERSUS IV MORPHINE FOR POSTOPERATIVE PAIN RELIEF IN CHILDREN

Authors: D.B. Andropoulos, M.D., R.W. Rowe, M.D., M.B. Heard, M.D.
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Introduction: Lumbar epidural morphine (MS) for postperative pain relief in children has been advocated for several years (1-4). However, no controlled studies comparing this route to conventional pain control have been published. The purpose of this study is to compare efficacy and side effects of lumbar epidural MS vs. intravenous (IV) MS for major surgery in children.
Methods: 14 children age 2-12 years have been studied. After research committee approval and informed consent from parents, patients undergoing laparotomy or thoracotomy were randomly assigned to receive either IV MS (0.2 mg/kg) or single shot lumbar epidural MS (0.075 mg/kg for laparotomy, 0.1 mg/kg for thoracotomy) during surgery. Postoperatively, nurses blinded to route of MS administration in the OR gave IV MS 0.05-0.15 mg/kg Q2h for pain score 4 or 5 on a 5 point pain scale (5): 1: Laughing, euphoric; 2: playful, content; 3: calm, asleep; 4: c/o mild/moderate pain; 5: c/o severe pain. Study duration was 48 hrs postop, and the groups were compared using unpaired T test, Fisher exact test, or Mann-Whitney U Test where appropriate, with $p<0.05$ considered significant.

Results: Table:

	IV (n=6)	Epid.(n=8)	
Time to 1st postop MS(hrs)	5.0±2.1	15.0±5.8	p=.002
MS mg/kg 1st 24 hrs	.53±0.17	.34±.23	p=.12
MS mg/kg 2nd 24 hrs	.29±0.25	.41±.22	p=.35
Vomiting	4	4	
Pruritis (req. Rx)	2	2	
Urinary retention	2	2	
Resp depression (PaCO2 > 50 or RR<16 in 2 y.o., <14 in 3-6 y.o., or <12 in 7-12 y.o).	0	2	p=.30

Mean pain scores per 6 hour period were not significantly different between groups.
Discussion: Single shot lumbar epidural MS provides longer lasting pain relief than IV MS in children after major surgery. However, using this protocol, supplemental IV MS doses and pain scores are not significantly different. Respiratory depression may be more common with epidural morphine.

References: 1. Anesthesiology 61:210-212, 1984.
2. Problems in Anesthesia 2:386-407,1988.
3. Mayo Clin Proc 59:530-533, 1984.
4. Anesthesiology 70:324-338,1989.
5. Anesth Analg 66:647-653,1987.

S10

Title: DO ASYMPTOMATIC INDIVIDUALS BENEFIT FROM PREOPERATIVE LABORATORY SCREENING OF COAGULATION STUDIES?

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Introduction: Many studies cite the incidence of abnormalities discovered by preoperative laboratory screening, but few studies segregate patients with test abnormalities by their histories alone. Accordingly, the incidence of abnormal results on laboratory screening tests for asymptomatic individuals is difficult to ascertain. The benefits of decreasing unproductive and possibly harmful testing are considerable. Among these are the avoidance of iatrogenic disease, postponements necessitated by further testing, anxiety provoked by extra tests and delays, and exponentially increased costs. We undertook this study to determine how often asymptomatic patients benefited from preoperative laboratory screening of coagulation studies.
Methods: With the approval of the Review Board of each institution and patient consent, patients completed an automated history questionnaire, HealthQuiz. This device provided a printout of suggestions for preoperative laboratory tests based on an algorithm using the patient's symptoms. Surgeons and/or anesthesiologists also ordered tests for each patient. Abnormal and significantly abnormal test results were prospectively determined and noted. Significantly abnormal results are those values outside of reported limits which might warrant treatment of a specific abnormality. On the day of surgery, the patient's anesthesiologist (different from the physician who ordered the tests and blinded to the method of test selection) was asked postoperatively whether abnormal test results had no effect on perioperative management or whether a change in management caused harm (i.e., increased anxiety, unnecessary risk of transfusion) or benefit (i.e., prevention of blood loss or epidural hematoma) to the patient.
Results: Of the 761 test results (platelet count, PT, PTT) from the *symptomatic* patients, 50 (6.6%) were abnormal, 15 (2.0%) were significantly abnormal, and 9 (1.2%) affected patient care. Of the 1,939 test results from *asymptomatic* patients, 61 (3.1%) were abnormal, 17 (0.9%) were significantly abnormal, and 5 (0.3%) affected patient care. Three (0.2%) asymptomatic patients were harmed, and no asymptomatic patient benefited from a change in care. Symptomatic patients had a significantly higher rate of test results that were abnormal, significantly abnormal, or that affected care than did asymptomatic patients (all $p \leq 0.01$) and a lower rate of test results that caused harm.
Discussion: This study suggests that clotting defects not detectable by thorough history are extremely rare. Furthermore, preoperative medical assessments including history appear to be much more effective and safer than indiscriminate preoperative laboratory testing as a means of screening for disease in asymptomatic individuals. Approximately 3 in every 2,000 individuals were harmed compared with none who benefited by the pursuit of abnormalities on their preoperative laboratory screening of coagulation studies.

S11

Title: **ASSESSMENT OF RENAL BLOOD FLOW DISTRIBUTION IN DOGS WITH CONTRAST ULTRASOUND FOLLOWING DOPAMINE INFUSION**

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Introduction: Changes in intra-renal blood flow distribution have been reported to be an early predictor of renal dysfunction,[1,2] but methods used to measure distribution have been inaccurate and associated with risks. Consequently, no true gold standard of measurement exists.[3] Recently, contrast ultrasound was used successfully to assess renal blood flow.[4] We hypothesized that contrast ultrasound techniques could be used to assess blood flow distribution in the canine renal cortex.

Methods: After approval from our Animal Care Committee, general anesthesia was induced and maintained with pentobarbital infusion in 10 dogs. The dogs' lungs were mechanically ventilated. Systemic and pulmonary artery pressures were continuously monitored. Continuous measurements of renal blood flow were obtained with an electromagnetic flow probe (EMFP). Ultrasound images of the kidney and aorta were obtained using a 3.0 MHz mechanical transducer placed directly on the renal capsule. Albunex®, a commercially prepared ultrasonic contrast agent, was injected into the thoracic aorta with an ECG gated mechanical injector. Contrast intensity was analyzed by ultrasound videodensitometry. Ultrasound images were acquired in a digital format using a 512 x 512 pixel mat with 256 gray level display. The contrast enhancement time measured for the aorta (input) was less than 10% of that measured for the kidney (inner or outer cortex). We thus calculated the relative blood flow ratio of inner to outer cortex from a mathematical formula based on classical dye dilution theory. The ultrasound system was calibrated to establish a relationship between contrast concentration and ultrasound intensity. Following low dose dopamine (2 μg/kg/min) or fenoldopam (selective DA$_1$ agonist) infusion, the relative change in renal cortical blood flow was determined. Changes in distribution were analyzed with Student's *t*-test with $p < 0.05$ considered significant.

Results:

Dogs	EMFP (ml/min)		Contrast (inner/outer)	
	Baseline	Dopamine	Baseline	Dopamine
6	162±31	197±48*	1.17±0.53	.54±0.26*
	Baseline	Fenoldopam	Baseline	Fenoldopam
4	179±26	233±26*	0.88±0.22	0.66±0.24*
* p<0.05				

Discussion: Contrast ultrasonography can be used to assess regional renal blood flow. A significant increase in the outer-to-inner cortical perfusion ratio was demonstrated in the canine kidney after low dose dopamine or fenoldopam infusion.

References:

1. Medicine 47:455-474, 1968
2. Am J Physiol 222:1125-1131, 1972
3. Scand J Clin Lab Inves 35:481-486, 1975
4. Anesth Analg 70:S10, 1990

S12

Title: **INTERCOSTAL NERVE BLOCK VERSUS GENERAL ANESTHESIA - SCORING OF POSTOPERATIVE PAIN**

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Introduction: The value of intercostal nerve block (ICNB) as an alternative to general anesthesia (GA) for minor breast surgery was demonstrated on previous occasions(1). It was of interest to evaluate postoperative pain relief comparing patients who received ICNB with those who were provided with a general anesthetic for lumpectomy.

Method: After institutional approval and patients' consent, 33 female patients (ASA I and II) were randomly assigned to four groups. In group A (n=8) ICNB was performed with plain bupivacaine 0.5%; group B (n=5) received lidocaine 2% with epinephrine (1:200.000) and group C (n=7) lidocaine 1.5% also with epinephrine (1:200.000). The local anesthetics were administered using a double blind schedule. Patients were placed in the prone position and four segments ranging from T3 to T6 were blocked with 4 ml of local anesthetic each. Intraoperative sedation was achieved with propofol given intravenously when necessary. In group D (n=13) GA was induced and maintained by propofol and alfentanil with O_2/N_2O delivered by face mask. Postoperative pain was recorded by an independant observer with a visual analogue scale (VAS) at 0, 15, 30, 45, 60, 90, 120, 180 and 240 minutes. Statistical comparisons were made by the Mann-Whitney U test. Chi square test was used to compare the patients demand for postoperative analgesics.

Results: All patients had adequate surgical anesthesia. The demographic data were similar in all groups. There were significant differences in the duration of operations particularly when comparing group A (58±5 min) with group D (32±3 min, $p < 0.0001$). Patients' postoperative pain score data are presented in the table. Significant differences could be demonstrated between group A and group D for the first three hours, as well as between groups B and D for the first hour following operation, further between groups A and B at 15 and between groups B and C at 15, 30, and 45 minutes postoperatively. Women with ICNB required significantly less analgesics than those who had a GA, i.e. 6 out of 13 patients at median 40 (range 15-315) min in group D in contrast to 5 out of 20 patients at median 120 (range 15-285) min in the other three groups ($p < 0.0001$).

Conclusions: A particularly longlasting postoperative pain relief was achieved with plain bupivacaine 0.5%, especially when taking into account the duration of operations in this group. Patients in the regional anesthetic groups required significantly less postoperative analgesics than those of group D.

Pain Scores (Mean ± SEM)

Time min	Group A	Group B	Group C	Group D
0	0.19 ∞ ± 0.11	0 #	1.56 ± 0.66	2.34 ±0.42
15	0.30 # ±0.14	0 # ø «	1.39 ±0.59	2.58 ±0.59
30	0.21 # ±0.12	0 # «	1.36 ±0.60	2.25 ±0.51
45	0.24 # ±0.14	0 # «	1.24 ±0.60	2.31 ±0.54
60	0.25 # ±0.15 ±0	0.18 ● ±0.14	0.91 ±0.48	1.87 ±0.53
90	0.34 ● ±0.23 «	0.82 ±0.56	0.86 ±0.35	1.54 ±0.50
120	0.43 ● ±0.40 +	1.14 ±0.75	2.30 ±1.31	1.00 ±0.40.
180	1.02 « ± 0.62	1.10 ±0.74	0.76 ±0.27	0.92 ±0.43
240	1.39 ±0.97	1.25 ±1.09	0.46 ±0.14	0.69 ±0.45

∞p < 0.001 v group D; # p < 0.01 v group D; ● p < 0.05 v group D
« p < 0.05 v group C; + p < 0.01 v group C; ø p < 0.05 v group A

1. Atanassoff PG, Alon E, Ziegler WH, Gautschi K, Pasch TH: Intercostal nerve block for minor breast surgery. Reg Anesth 1991:16, 23-27

S13

Title: EFFECTS OF INTRAVENOUS OMEPRAZOLE AND RANITIDINE ON GASTRIC pH DURING GENERAL ANESTHESIA

Authors: P.G. Atanassoff MD, E. Alon MD, R. Zimmermann MD,
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Introduction: Aspiration of gastric contents into the lungs is one of the most feared complications in anesthesia. Damage occurs when the pH is lower than 2.5. The goal of this clinical study was to investigate the increase of gastric pH under the influence of iv omeprazole and ranitidine.

Methods: After ethic`s commitee approval and patients` consent 47 ASA class I and II patients were randomly assigned to five groups. Following induction of general anesthesia group 1 (n=8) received omeprazole 40 mg iv, group 2 (n=10) omeprazole 80 mg iv, group 3 (n=9) ranitidine 50 mg iv and group 4 (n=9) ranitidine 100 mg iv. The control group did not receive either of the two drugs. All patients were provided with a nasogastric electrode connected to a gastrograph (Mark III, Fresenius). Data were continuously recorded over a period of two hours and presented as mean ± SEM. Statistical analysis was performed using the Mann-Whitney U test with $p < 0.05$ considered significant.

Results: Patients` characteristics were similar in the five groups. The table presents gastric pH values over a two hours` time . There was a significant increase in gastric pH in all four medicated groups (s.Table). Also there were significant differences in the four groups when compared with the control group.

Discussion: The data suggest that omeprazole and ranitidine administered intravenously during general anesthesia cause a continous increase in gastric pH. This increase did not differ significantly either between the two drugs or the different doses used in our study.

Gastric pH Data (Mean ± SEM)

TIME (min)	Control (pH)	Omeprazole 40 (pH)	Omeprazole 80 (pH)	Ranitidine 50 (pH)	Ranitidine 100 (pH)
0	**0.93**	**1.16**	**1.06**	**1.32**	**1.32**
	±0.18	±0.18	±0.09	±0.21	±0.17
20	**0.95**	**2.23** *	**2.01** *	**1.88**	**2.42** +
	±0.06	±0.55	±0.32	±0.31	±0.38
40	**1.12**	**3.00** *	**3.68** *	**3.35**	**3.56** *
	±0.14	±0.62	±0.45	±0.63	±0.66
60	**1.18**	**4.09** *	**5.50** *	**4.25** +	**4.81** *
	±0.17	±0.65	±0.53	±0.74	±0.54
80	**1.28**	**4.88** *	**6.02** *	**5.03** *	**5.40** *
	±0.23	± 0.65	±0.49	±0.68	±0.46
120	**1.15**	**6.46** *	**6.91** *	**6.68** *	**6.43** *
	±0.06	±0.17	±0.20	±0.25	±0.30

* $p < 0.01$ + $p < 0.05$
versus control

S14

TITLE: THE EFFECT OF PROPOFOL ON MYOCARDIAL CONTRACTILITY AND FUNCTION IN NORMOVOLEMIC AND HYPOVOLEMIC SWINE

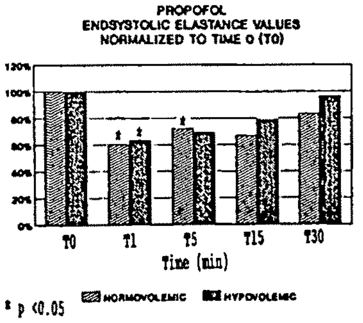
AUTHORS: J.J. Baeuerle, M.D., C.P. Kingsley, M.D., J.A. Ward, Ph.D., D. Williams and J. Hinds

AFFILIATION: Anesthesia Department, Brooke Army Medical Center, Ft. Sam Houston, TX 78234-6200

Propofol is a new intravenous anesthetic with the advantages of rapid, smooth emergence from anesthesia, short duration and lack of accumulation. This study assesses the effect of propofol on myocardial contractility in normovolemic and hypovolemic swine using the end-systolic pressure-dimension relationship (ESPDR).

Under an approved animal use protocol, two groups of Yorkshire swine weighing 15-25 kg were anesthetized, intubated and mechanically ventilated. Two sonomicrometer crystals were placed in the A-P dimension of the left ventricle (LV) and a 5mm pressure transducer was placed through the LV apex. A snare was placed around the inferior vena cava (IVC) to vary preload. Pressure-dimension (PD) loops were generated while occluding the IVC. End systolic elastance (Ees), an index of myocardial contractility, was calculated as the slope of the linear-regression line through a series of end-systolic pressure-dimension points during IVC occlusion. After baseline control (BC) measurements were obtained, Group A (n=10) swine were hemorrhaged to a MAP of 40 mmHg. When a steady state had been reached hemorrhage control (HC) measurements were made. Propofol, 5 $\text{mg}\cdot\text{kg}^{-1}$, was given as an IV bolus. The normovolemic swine, Group B (n=5), were also given propofol 5 $\text{mg}\cdot\text{kg}^{-1}$ after BC measurements had been made. Measurements were made at 1, 5, 15 and 30 minutes (T1, T5, T15 and T30) after propofol injection. Data was analyzed with a repeated measures ANOVA and a Bonferroni corrected t-test. A p value <0.05 was considered statistically significant.

Propofol significantly depressed MAP at T1, T5 and T15 in both Groups A and B. Ees was significantly reduced at T1 and T5 in both Group B and at T1 in Group A. SVR was significantly depressed at T1 and T5 in Group B. In this model, an induction dose of propofol decreased MAP by causing a depression of myocardial contractility as well as a reduction of afterload.



S15

Title: **Pulse Oximeter Failure Rates: Effects of Manufacturer, Sensor Site, and Patient**

Authors: SJ Barker, Ph.D., M.D., J. Hyatt, B.S., WA Rumack
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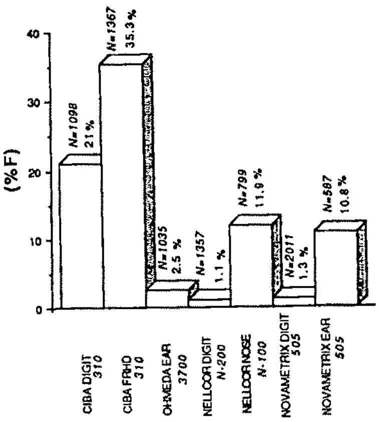
INTRODUCTION: Pulse oximetry is a standard of care during anesthesia. Pulse oximeters will fail to determine an SpO2 value under circumstances that reduce signal-to-noise ratio, including low cardiac index, extremes of SVR, hypothermia, and anemia (1). A clinical study showed an average failure rate of 1.24% for a finger sensor in the operating room (2). We have shown previously that earlobe sensors have a higher failure rate (5.8%) (3). We present here a study of the failure rates of seven different pulse oximeters in the operating room, showing effects of model, sensor site, and patient variables.
METHODS: Prospective data were obtained from 111 surgical patients, following institutional review approval. The seven pulse oximeter sensors were applied before induction of anesthesia, and data were recorded every five minutes thereafter. Each data set included pulse oximeter SpO2 and heart rate, vital signs, PetCO2, PtcO2, and ventilator settings. The overall percentage failure rate (%F) was calculated for each sensor by dividing the number of "failed" readings (no SpO2 value) by the total. A %F was also calculated for each patient to study the influence of patient variables. The significance of patient variable effects was determined by ANOVA.
RESULTS: Figure 1 shows the overall %F of the seven pulse oximeter and sensor combinations for 111 patients, 800 - 2,000 data points per sensor. The finger transmission-sensors (Nellcor N-200, Novametrix 505) showed low failure rates: 1.1% and 1.3%. The Ohmeda ear sensor had a lower %F (2.5%) than the Novametrix ear (10.8%) or Nellcor nose (11.9%). The Ciba reflectance sensors on either the digit or forehead had much higher %F.
DISCUSSION: Pulse oximeter failure rates in the operating room depend upon sensor site, with transmission finger sensors yielding the best overall results (%F = 1.1-1.3%). Ear and nose sensors have a higher mean %F, and the newer forehead reflectance sensors appear to have an unacceptable failure rate in their present form. Failure rate is not significantly dependent upon ASA physical status.

REFERENCES.

1. Anesthesiology 63, 3A: A175, 1985.
2. Anesth Analg 70, 2S: S289, 1990.
3. J Clin Mon 7, 1: 102, 1991.



S16

Title: SEQUESTRATION OF VECURONIUM DURING EXTREMITY SURGERY INVOLVING USE OF A THIGH TOURNIQUET

Authors: RE Barnette MD, LI Eriksson MD, NW Brister MD, GF Cooney PharmD, N Johanson MD, C Carlsson MD
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Introduction:

Many lower extremity surgical procedures make use of pneumatic tourniquets. Information is limited regarding the pharmacokinetics and pharmacodynamics of anesthetic drugs, administered prior to inflation of the tourniquet, which are sequestered in the extremity and then subsequently released into the general circulation following deflation of the tourniquet (1). The purpose of this study was to determine whether the application of a pneumatic tourniquet, with vascular occlusion effected the pharmacokinetics and pharmacodynamics of vecuronium.

Method:

Eight otherwise healthy patients (ASA II, age 55-79) scheduled for total knee replacement agreed to be studied. Informed concent and human subject committee approval were obtained. Anesthesia was induced with pentothal 3-4 mg/kg and fentanyl 1-3 μg/kg. Intubation was accomplished using succinylcholine and anesthesia was maintained with 0.5 % (end-tidal) isoflurane in nitrous oxide and oxygen (70/30). All patients were mechanically ventilated and maintained normocarbic. Core temperature was normal and peripheral skin temperature was kept >32.0 °C throughout the study.

Five minutes prior to inflation of the tourniquet vecuronium 0.1 mg/kg i.v. was administered. Serial arterial blood samples were drawn for measurement of vecuronium levels and subsequently frozen to await further analysis.

Neuromuscular function was measured in the adductor pollicis muscle after supramaximal train-of-four stimulation (2 Hz for 2 sec every 12 sec) using a Myograph 2000 neuromuscular transmssion analyser. The rate of twitch recovery was expressed as the change in the first twitch of the TOF response and was measured at three time intervals: 2, 5 and 10 min prior to and after release of the tourniquet. The rate of recovery was compared before and after release of the tourniquet using the paired Student's t-test.

Results:

Table 1: The rate of twitch recovery prior to and after release of a thigh tourniquet in eight patients having received vecuronium. Data are expressed as mean ± SD, (* P<0.01).

	Rate of twitch recovery (%)	
Time duration	*Prior to release*	*After release*
2 min	3.0 ± 1.4	0.6 ± 1.7*
5 min	6.3 ± 3.3	2.7 ± 3.1*
10 min	10.0 ± 3.4	4.6 ± 3.7*

Pharmacokinetic analysis of vecuronium plasma concentrations were not yet available.

Discussion:

Previous studies have shown that clinically relevant amounts of benzodiazepines and/or opiates may be released from a lower extremity after deflation of a tourniquet (1). We therefore questioned whether an increased neuromuscular block (i.e. recurarization) with vecuronium may occur by a similar mechanism. Our data suggests that recurarization occurs after release of the tourniquet. The magnitude of change was, however, small and therefore appears to be of limited clinical importance.

References:

1. Acta Anaesthesiol Scand 34: 104-108, 1990

S17

Title: Onset of Neuromuscular Blockade: A Comparison of Intra-arterial and Intravenous Vecuronium

Authors: RR Bartkowski MD PhD, C Wilkerson MD,
R Epstein MD, A Marr CRNA, H Schieren PhD

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The development of new rapid onset non-depolarizing neuromuscular blockers has stimulated interest in factors determining blockade onset. Since intra-arterial injection bypasses transport delays, it can provide a measure of delays at the tissue level. This study was designed to compare onset delays between intra-arterial and intravenous administration. Blood levels of vecuronium were also measured from a vein draining the area to determine initial concentration and the length of time drug persist in the tissue.

Methods: Five patients having radial arterial catheters for surgery gave written informed consent to this IRB approved study. Anesthesia was induced with thiopental (300-500 mg/kg) and fentanyl (3 - 8 ug/kg). Intubation was accomplished under isoflurane and N2O/O2 without muscle relaxant. When isoflurane had been off at least 20 minutes (0.1% or less ET), an intra-arterial bolus of vecuronium (0.25 - 1 mg) was given. The force of thumb adduction, after stimulation of the ulnar nerve at the wrist, was measured by train-of-four every 12 sec. Blood samples were drawn from a nearby vein over the next 20 min. Samples were analyzed by capillary gas chromatography (sensitivity: 20 ng/ml and CV: 10%).

Control values for intravenous administration were taken from a previously studied group of 7 patients receiving vecuronium and similarly measured.

Results: Patients averaged 44 ± 17 yrs and 85 ± 4 kg. Blockade onset was more rapid than seen after intravenous administration (Table 1). Block development was qualitatively different. Fade developed more slowly than seen after intravenous administration with similar final twitch depression. Train-of-four ratio remained elevated while T1 depression progressed (Table 1). Blood levels of vecuronium decayed rapidly, following a exponential curve with T½ of 1.5 ± 0.5 min. Measured initial concentrations of vecuronium ranged from 5,000 to 10,000 ng/ml.

Discussion: The onset of neuromuscular blockade after intra-arterial injection was rapid. However, there was still a significant delay in initial onset to 5% blockade. If intravenous administration is associated with a transit delay of 0.5 min then the two are comparable. Full development of block developed much faster after intra-arterial injection but blood levels were also much above typical reported intravenous values. Qualitative differences in twitch vs train-of-four can arise from the different concentration profiles (high concentration-rapid decay vs lower concentration-slow decay). It appears that differences in onset time are determined partly by transit and concentration, but the major delay appears at the tissue level and is likely a drug specific property.

Table 1

		Time(min) to % of Maximum Block			T4/T1@ T1 of	
Site	T1%	5%*	50%*	90%*	40%	25%
Arterial	26.3	0.48	0.73	1.39	0.77	0.75
	(29.4)	(0.44)	(0.56)	(0.53)	(0.7)	(0.13)
I.V.	16.8	1.49	2.51	4.01	0.51	0.35
	(24)	(0.62)	(0.69)	(0.59)	(0.11)	(0.12)

All values mean (SD)
*Significant difference between injection site.

S18

TITLE: CALCIUM CHANNEL AGONIST EFFECT ON HALOTHANE DEPRESSION OF MYOCARDIAL CALCIUM CURRENT IN GUINEA PIGS

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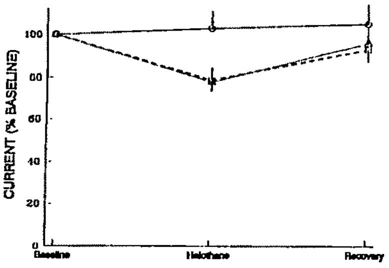
INTRODUCTION: The inhalational anesthetics are known to inhibit transsarcolemmal Ca^{2+} entry into myocardial cells (1-3). The mechanism of this inhibition is not well understood. The whole cell configuration of the patch clamp was utilized to evaluate whether the dihydropyridine Ca^{2+} channel agonist BAY K8644 would abolish or decrease the inhibition of Ca^{2+} entry caused by a clinically relevant level of halothane.

METHODS: Single ventricular myocytes were obtained from enzymatically dissociated guinea pig hearts and voltage clamped in the whole cell configuration. Calcium currents were evoked by stepwise sequential 10 mV depolarizing potentials to from -50 to +40mV from a holding potential of -80mV at baseline, at the end of a 3 minute exposure to external solution equilibrated with air (group 1, control cells) or 1% halothane (groups 2 & 3) and following a 3 minute recovery. Group 3 had in addition 5µM BAY K8644 in all external solutions. Only data from cells showing recovery in current following exposure to halothane were included for analysis.

RESULTS: Baseline peak calcium current was similar in groups 1 (185±37 pA/cm^2; mean±SE, N=5) and 2 (206±22 pA/cm^2, N=12) and higher in group 3 (311±38 pA/cm^2, N=10) (P<0.04). There were no changes in current in group 1 with exposure to non-halothane containing solution or with recovery. With exposure to halothane, current decreased equally to 79±5% in group 2 cells and to 78±6% in group 3 cells (P<0.01 vs baseline)(Fig 1).

DISCUSSION: Although peak calcium currents in BAY K8644 cells were consistently higher, the relative inhibition of current induced by halothane was identical to cells not exposed to BAY K8644. The ability to selectively inhibit the myocardial depression of an anesthetic without affecting anesthetic potency is attractive. The calcium channel agonist BAY K8644 cannot selectively ameliorate the inhibition of calcium current in myocardial cells caused by halothane, and presumably by other inhalational anesthetics.



REFERENCES: 1. Acta Anaesthesiol Scand 29:583-586, 1985.
2. Anesthesiology 69:742-749, 1988.
3. Anesthesiology 74:340-345, 1991.

S19

TITLE: NAUSEA, VOMITING, AND NARCOTIC USE IN OUTPATIENTS WHO UNDERGO KNEE ARTHROSCOPY UNDER SPINAL AND GENERAL ANESTHESIA

AUTHORS: C.L. Baysinger, M.D., E.A. Bowe, M.D., L.A. Sykes, M.D., L.S. Bowe, M.S.N.
AFFILIATION: Department of Surgery/Anesthesiology, University of South Carolina School of Medicine, Richland Memorial Hospital, Columbia, South Carolina 29203

It is unclear whether the administration of perioperative narcotics increases nausea and vomiting (N/V) in patients who undergo outpatient (OP) surgery. We compared rates of N/V in patients who received perioperative narcotics (NARCS) for knee arthroscopy (ARTH) under spinal (SAB) and general anesthesia (GA) versus those who did not.

After approval of the Institutional Review Board, we reviewed the anesthesia, operating room (OR), recovery room (RR), and OP records of 134 patients who had ARTH. Age, sex, ASA classification, NARCS used in OR, RR, and OP and N/V in RR and OP were recorded. Unpaired t-test, Chi square, and Fischer's Exact Test were used.

Table 1 summarizes demographic data, overall NARCS used, and N/V. Table 2 details N/V between NARCS and no NARCS groups. Patients who received SAB were older, had no postoperative N/V, and required less postoperative NARCS than those who received GA. Patients who received GA had higher rates of N/V when compared to SAB. Patients who received intraoperative NARCS for GA had more N/V when compared to patients who did not receive any NARCS during GA.

We conclude that the use of SAB for ARTH is associated with a low incidence of N/V in outpatients and that the use of perioperative NARCS does not increase N/V in this group. N/V is higher in patients who receive GA, increases when NARCS are used intraoperatively, but may not increase when NARCS are used postoperatively for pain control.

Table 1 Demographics

	SAB	GA
Patients #	66	68
Sex (% female)	27%	37%
Age *	43±15	32±16
ASA	1.9±.8	1.6±.7
NARCS in OP & RR **	27%	66%
Postop N/V ***	0%	40%

*p<.05 compared to GA
**p<.01 compared to GA
***p<.001 compared to GA

Table 2 Nausea, Vomiting, and NARCS

	SAB #	N/V	GA #	N/V
NARCS-OR Only	46	0% **	17	47% *
NARCS-Postop Only	12	0%	6	17%
No NARCS	16	0%	8	0%

*p<.05 compared to no NARCS in GA Group
**p<.001 compared to GA

S20

Title: ANALGESIC EFFICACY OF KETOROLAC IN POSTOPERATIVE PEDIATRIC PATIENTS

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Introduction: Pediatric patients often receive inadequate postoperative analgesia due to misperceptions about pain and fear of respiratory depression[1,2]. Meperidine or morphine, which are most commonly used, have a significant rate of adverse side effects which limit their usefulness in outpatient surgery. Ketorolac tromethamine is a nonsteroidal anti-inflammatory cyclo-oxygenase inhibitor with potent analgesic properties and moderate anti-inflammatory effects[3]. Bioavailability is 100% following i.m. administration with an elimination half-life of 5.7 ± 1.8hrs in children[4]. It has been shown to be an effective perioperative analgesic in adults[5]. Bleeding times are slightly prolonged after several doses[6]. The aim of this study was to determine whether ketorolac is an effective perioperative analgesic for children and whether significant prolongation of bleeding time occurred.

Methods: After institutional review board approval and informed consent, 18 ASA 1 and 2 children aged 1-10 yrs scheduled for procedures which would normally require perioperative narcotic analgesics were randomized into 1 of 3 treatment groups in a double blind prospective manner. Following a standardized mask induction, a bleeding time was performed and the study medication administered i.m. Group I received ketorolac 0.75 mg/kg; Group II meperidine 1 mg/kg and Group III normal saline. A trained research RN performed all tests and assessments. CHEOPS scores were assigned in PACU at 5,10,15,30,45,60 and 120min. Meperidine 0.5 mg/kg i.v. was given for CHEOPS ≥9. Repeat bleeding times were measured 180min post-injection.

Results: N=6 for each group. Median pain scores at 10min were 9 and 10 for the placebo and merperidine groups, respectively, and 7.5 for the ketorolac group. Pain scores were ≤8 and comparable between the groups at 60 and 120min. 3/6 patients in the meperidine group and 2/6 in the ketorolac group required narcotics in the first hr in PACU while 6/6 placebo patients required narcotics. Placebo patients required twice as much narcotic to achieve similar scores. Bleeding times were comparable between groups and did not demonstrate an increase. Mean bleeding time was 3.5 ± 1.3min before and 3.6± 1.5min 3hrs after treatment. Nausea and vomiting occurred with equal frequency in each group.

Discussion: Ketorolac 0.75 mg/kg provided postop analgesia which was comparable to that provided by meperidine without respiratory or CNS depression. Risk of bleeding was not increased. When narcotics were required, analgesia was achieved with lower doses.

References: 1)J Ped 113;421,1988 2)Pediatrics 77:11,1986 3)Eur J Clin Pharmacol 36S:3,1989 4)Eur J Clin Pharmacol 35:423,1988 5)Pharmacotherapy 6:253,1986 6)Clin Pharmacol Ther 43:542,1988

S21

Title: THE EFFECT OF PROPOFOL ON THE HUMAN PUPILLARY LIGHT REFLEX

Authors: K Belani, M.D., J Hynson, M.D., DI Sessler, M.D., M Larson, M.D., J McGuire, B.S., B Merrifield, B.A., D Washington, M.D., D Crankshaw, F.F.A.R.A.C.S., Ph.D.

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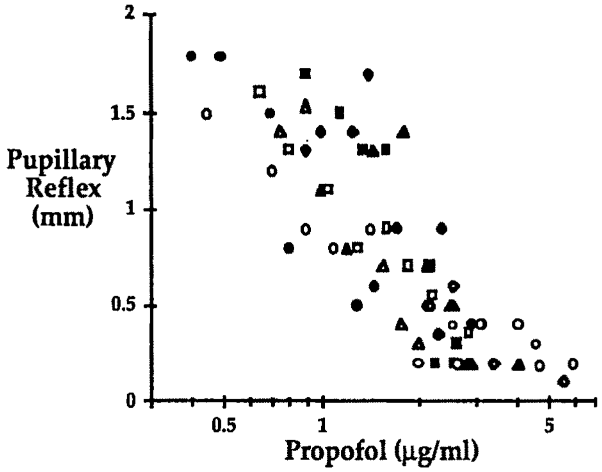
Evaluation of anesthetic level is often difficult during intravenous anesthesia. We tested the correlation between plasma propofol concentration and the pupillary light reflex in eight volunteers. They were anesthetized with a 2-2.5 mg/kg injection of propofol, then given vecuronium to facilitate tracheal intubation. Anesthesia was continued with an 80-150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion of propofol and 70% N_2O. Central hypothermia to approximately 33°C was induced as part of a separate study on post anesthetic shivering. We have previously demonstrated that mild central hypothermia does not diminish pupillary responses.[1] N_2O was discontinued after 2-3 h, residual neuromuscular blockade was antagonized with neostigmine and glycopyrolate, and the trachea's extubated. When the end-tidal N_2O concentration decreased to < 15%, the propofol infusion was discontinued. Arterial blood for propofol analysis was sampled at 0, 2.5, 5, 10, 20, 30, 45, and 60 min after propofol was discontinued. Pupillary light reflexes were simultaneously measured using a portable infrared pupillometer (Fairville Medical Optics, Inc). Propofol produced a dose-dependent decrease in the light reflex amplitude (Fig.). Arterial propofol levels above 3.0 µg/ml produced small reflexes, but the light reflex was never totally abolished. We conclude that the pupillary light reflex is a sensitive measure of plasma propofol concentration.



Legend: The relationship between plasma propofol concentration and the pupillary light reflex. Each symbol represents values from one volunteer.

Reference: 1) Anesthesiology 75:62-67, 1991.

Supported by NIH grant #R29 GM39723.

S22

Title: DOES CARDIAC OUTPUT MEASUREMENT CHANGE THE CLINICAL DECISION?

AUTHORS: P.F. Benson FFARCSI, M.G. Coughlan FFARCSI, K. Flynn FFARCSI, D. Phelan FFARCSI

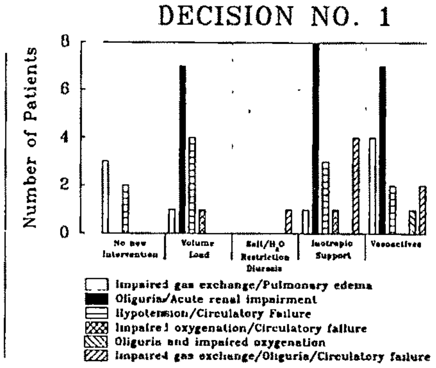
AFFILIATION: Mater Hospital, Dublin, Ireland

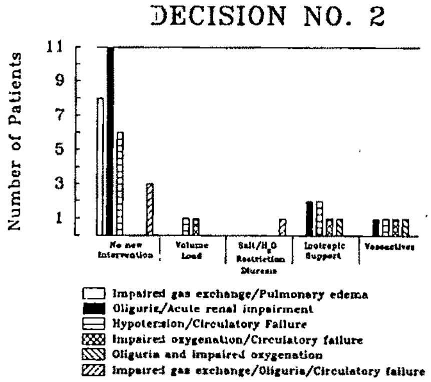
Introduction: We believe that measurement of pulmonary artery pressures and a careful clinical assessment offer the maximum benefit in the use of Swan-Ganz catheters. We therefore designed a prospective analysis to test this hypothesis.

Methods: 35 patients were studied. A data sheet recording population characteristics and clinical features was completed pre-catheterization. Pulmonary artery pressures were recorded and a therapeutic decision made. Cardiac output and derived indices were then measured and a second therapeutic decision made. The difference between the first and second decisions was then analyzed.

Results: Cardiac output measurement altered clinical therapy in 20% of patients.

Discussion: Cardiac output estimation is time consuming and increases the demands placed on medical and nursing personnel and adds to the cost of patient care. 80% of patients in this study received no additional benefit from this maneuver.





S23

Title: LIPOSOME ENCAPSULATION PROLONGS ALFENTANIL SPINAL ANALGESIA IN THE RAT

Authors: CM Bernards, M.D.*, T Luger, M.D*., T LYaksh, Ph.D.^, HF Hill, Ph.D.*
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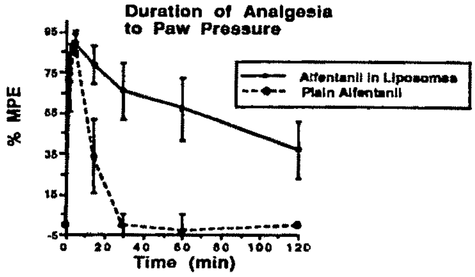
^Univ. of Calif.,San Diego, San Diego, CA.

Introduction: Intrathecal morphine provides profound pain relief, however, morphine, undergoes rostral spread in the CSF to reach brain opiate receptors where it produces significant side effects (e.g., respiratory depression). The phenylpiperidine-derived opioids (e.g., alfentanil) are less likely to spread rostrally, but their short duration of analgesia makes them unsuitable for "single shot" intrathecal use. To overcome this deficiency of phenylpiperidine opioids we encapsulated them in liposomes to extend their duration of analgesia.

Methods: Alfentanil-encapsulated liposomes were prepared by dissolving dipalmitoylphosphatidyl choline (190mg) and cholesterol (50 mg) in chloroform and rotary evaporating the solution to dryness. Alfentanil (50mg) in 2 ml saline was added to the lipid film and agitated at 60°C for one hour. The resultant liposomes were separated from unencapsulated drug by ultracentrifugation. Animal studies were approved by the UCSD Animal Care Committee. Intrathecal catheters were implanted in 14 male Sprague-Dawley rats (250-300g) under halothane anesthesia. One week after surgery, the rats were divided into two groups; one group received 30μg plain alfentanil (10μl) and the other received 30μg alfentanil encapsulated in liposomes (10μl). Nociceptive testing was performed before and immediately after intrathecal injection using hotplate and paw pressure tests. The end point for the hotplate test was hindpaw licking or an attempt to escape the plate. The endpoint for the paw pressure test was withdrawal of the hindlimb from the testing device. To prevent injury, animals were removed from the hotplate after 60 seconds if they did not respond and paw pressure was limited to 400 grams. Hotplate latencies were determined as the time required for a response while paw pressure latencies were determined as the maximum pressure tolerated by the animal. Latencies for both tests were converted to a percentage of the maximum possible effect (%MPE) using the following relation: %MPE=[(post drug latency-predrug latency)/(cutoff latency-predrug latency)] x 100. The plot of %MPE vs time for each test was used to calculate the area under the time - effect curve (AUC).

Results: Maximal analgesia (as %MPE) did not differ between plain and liposome encapsulated alfentanil groups for either test of analgesia (hotplate test, plain: 79±13 %MPE, liposome: 62±14 %MPE; paw pressure test, plain: 90±6 %MPE, liposome: 89±4 %MPE). The paw pressure AUC was 1023 %MPE-minutes for plain alfentanil and 6925 %MPE-minutes for alfentanil encapsulated in liposomes ($p<0.05$). The Hotplate AUC was 984 %MPE-minutes for plain alfentanil and 3824 %MPE-minutes for alfentanil encapsulated in liposomes ($p<0.05$). A graph of the paw pressure data appears in figure 1.

Discussion: The data indicate that liposome encapsulation significantly prolongs alfentanil spinal analgesia in the rat without diminishing the intensity of the analgesia. The prolonged analgesia in the liposome group is probably due to slow release of opioid into CSF. With liposome encapsulation it may be possible in the future to produce selective spinal analgesia with phenylpiperadine-derived opioids which lasts as long as does morphine analgesia but avoids the side effects associated with rostral spread.



S24

Title: PREOPERATIVE GLYCOPYRROLATE: PO, IM, OR IV ADMINISTRATION?

Authors: C Bernstein MD, M Torjman MEd, D Ritter MD

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Introduction: Painful and anxiety-provoking IM injections of glycopyrrolate (GLY) have been used for decades as a preanesthestic antisialogogue and vagolytic. PO administration may be a more desirable alternative. To assess the effectiveness of different routes of administration, we compared PO, IM and IV GLY *vs.* placebo.

Methods: 38 ASA I-II patients scheduled for elective surgery gave informed written consent to participate in this IRB approved study. In a randomized double blind fashion, we compared GLY 2.0mg PO (n=9), 0.2mg IM (n=10), 0.2mg IV (n=10) *vs.* placebo (PO, IM, IV) (n=9). PO and IM GLY were administered approximately 90 mins prior to surgery. IV GLY was given in the holding area prior to surgery. Anesthesia induction and maintenance were standardized. Patients subjectively assessed oral dryness; the anesthesiologist rated intubating conditions as optimal or sub-optimal. Gastric contents were continuously suctioned through an orogastric tube and measured for volume and pH. Oral secretions were weighed using absorbent packing. Heart rate and BP were recorded preinduction, 1, 2 and 5 min post intubation. Data was analyzed using ANOVA and Kruskal Wallis tests; $p<0.05$ was considered significant.

Results: There were no significant differences in age, weight, ASA status or length of surgery between the groups. There were no significant differences between the groups with respect to the patients' sensation of dry mouth, the anesthesiologist's rating of intubating conditions (Figure 1), gastric pH, blood pressure, or heart rate. In the PO GLY group, oral and gastric volumes were not significantly different than placebo. IM GLY significantly decreased oral secretions. IV GLY significantly decreased both oral and gastric secretions (Figure 2).

Figure 1.

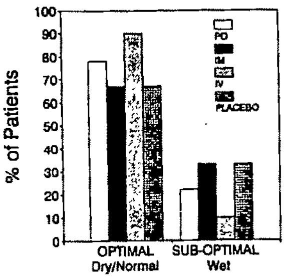
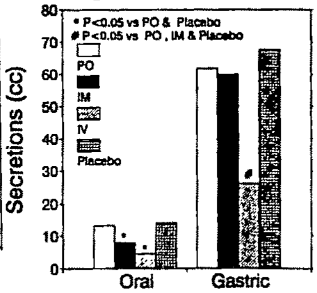


Figure 2.



Discussion: We found that PO GLY had no benefit over placebo. IM GLY significantly decreased oral secretions, but had no effect on gastric secretions or intubating conditions. Patients in the IV GLY group had significantly decreased oral and gastric secretions; 90% of the patients in that group had optimal intubating conditions and no patient rated his mouth as uncomfortably dry. IV GLY administered in the holding area appears to be more effective in reducing oral and gastric secretions compared to the other routes of administration.

S25

TITLE: **INTRATHECAL LIDOCAINE /MORPHINE INFUSION FOR POSTOPERATIVE PAIN ABLATION**

AUTHORS: **BRIAN K. BEVACQUA, M.D.**
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INTRODUCTION

Intrathecal infusions (ITI), utilizing lidocaine (L) alone[1] or in combination with fentanyl[2], have proven to be a safe and effective alternative to epidural infusions when major conductive analgesia is indicated. However, problems exist with the ITI of these agents, either alone or in combination. Long-term (hours to days) L administration has been associated with nerve injuries in animals and may cause similar problems in humans. Use of IT narcotics alone may produce analgesia, but will not effect ongoing surgical stress. Initial attempts to combine these agents were associated with increasing complications (temporary lower extremity sensory and motor dysfunction) and less effective analgesia[2]. In an attempt to maximize analgesia and stress ablation while minimizing complications, we studied the combination of L and morphine(M) for ITI.

MATERIALS AND METHODS

The patients, all scheduled for vascular procedures with planned postoperative SICU admissions, were informed of their anesthetic options, and gave informed consent to an IRB approved study. All patients in whom aortic surgery was anticipated had macrospinal catheters ($\geq$20 gauge) and all others had microspinal catheters (28 gauge CoSpan Kendall) placed. IT infusions were begun as soon as lower extremity motor tone returned to normal after surgery. The initial infusion consisted of 0.1% L with the M component (preservative free) adjusted to provide 0.5 mg /24 hours. Rate was set 3cc/hr for micro- and 10cc/hr for macro-catheters. All patients had parenteral narcotics available if needed. The following parameters were recorded: age, sex, ASA PS , subjective (patient complaints/nurse comments) and objective (physical exam, laboratory data) observations, supplemental analgesics employed, total infusion time, as well as neurologic, respiratory or cardiovascular complications attributed to IT infusions.

RESULTS

Twenty-four patients, all male, underwent 26 surgical (14 aortic reconstructions, 12 peripheral) procedures. They had a mean age of 66.6 years (range 48-78) and mean ASA PS of 3.9. 9 patients had micro- and 17 had macrospinal catheters placed. Attempts to produce additional analgesia by increasing the L portion of the infusion (from 0.1 to 0.2 %) produced (temporary) lower extremity sensory and motor deficits without improved analgesia. It was decided instead to increase the M portion, (if pain was diffuse) and/or the rate (if pain was limited to the extremities of the surgical incision). This produced improved analgesia without any change in neurologic baseline.

Mean infusion time was 48.6 hours (range 3 to 120). Mean 24 hour M dose received was 1.3 mg (range 0.5 to 3.0 mg). 18 patients required no supplemental analgesics while 8 patients received (a mean dose of) 10 mg of intravenous morphine (mean infusion time - 46.2 hours). 1 patient also received acetominophen and 1 received ketorolac with good results. 4 infusions were interrupted due to new onset lower extremity sensory or motor deficits. 2 patients had returned to normal function in 2 hours and had their infusions restarted at a reduced rate (10-8 cc), without further problems. 1 patient returned to the OR for an occluded vascular graft. After extensive workup, 1 patient was diagnosed as having suffered a spinal cord infarction. 1 infusion was terminated after three hours due to hemodynamic instability, which did not appear to be related to his infusion. 1 patient received a single dose of Narcan for pruritis 10 hours after his IT infusion had been terminated.

DISCUSSION

Postoperative IT infusions provide analgesia equal to that seen with epidurals, but may be superior at ablation of surgical stress (when a local anesthetic is included)[3]. Low dose L (<10 mg./hour) was not associated with neurologic problems when infused with a wide range of M doses (0.5-3mg/24 hours). Increased patient activity, especially coughing and deep breathing after aortic surgery, necessitated these larger than expected amounts of M, producing excellent analgesia without neurologic, hemodynamic, or respiratory complications. Hence, the combination of L/M for IT infusions appears to be a safe and effective way to provide postoperative analgesia and surgical stress ablation.

REFERENCES:

1. Anesthesiology 1990; 73: A833.
2. Anesthesia Analgesia 1991; 72: S20
3. Br. J. Anaesth 1989; 63: 189-95.

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S26

Title: FRUCTOSE-1,6-BISPHOSPHATE (FBP) DECREASES Ca^{++}_i IN RAT NEURONS AND ASTROCYTES DURING ANOXIA

Authors: P.E. Bickler, MD, PhD., J. Kelleher, PhD, and G.A. Gregory, M.D.

Affiliation: Departments of Anesthesia and Neurology, Univ. Calif., San Francisco, CA.

Introduction: Elevation of intracellular calcium (Ca^{++}_i) may be a cause of cell death during cerebral ischemia or hypoxia (1). FBP reduces cellular injury resulting from ischemia or hypoxia in brain (2), cultured astrocytes (3) and heart (4). We investigated the possibility that one neuroprotective effect of FBP may be to reduce the increase in Ca^{++}_i during anoxia. Cortical brain slices and cultured astrocytes from rats were used as models of CNS hypoxia.

Methods: 350 µm cortical brain slices or monolayer cultures of astrocytes from 1 day old rats were incubated in Earl's balanced salt solution containing 5.6 mM glucose and 10 mM HEPES buffer, pH 7.4, bubbled with 95% O_2, 5% CO_2. The cells were loaded with a Ca^{++} sensitive dye (5µM Fura-2) for continuous measurement of Ca^{++}_i with a fluorescence spectrophotometer. During study, the cells were housed in a cuvette perfused with Earl's solution equillibrated with 95% O_2/ 5% CO_2. Ca^{++} uptake in hypoxic astrocytes was also measured with ^{45}Ca.

Results: During simulated anoxia (treatment with 100 µM cyanide to block oxidative ATP production), a large sustained increase in Ca^{++}_i occurred in both astrocytes and brain slices. 3.5 mM FBP significantly reduced both the intensity and duration of the increase in Ca^{++}_i during cyanide treatment in brain slices, and also in hypoxic astrocytes studied with ^{45}Ca. Calcium ionophore caused large increases in Ca^{++}_i in brain slices and astrocytes. EGTA (a Ca^{++} chelator) reduced Ca^{++}_i during treatments to increase cell Ca^{++} permeability (ionophores, detergents) in both cortical slices and astrocytes.

Discussion: We conclude: (1) Increases in Ca^{++}_i result from cellular energy failure, (2) FBP attenuates the increase in Ca^{++}_i that results from blockade of oxidative ATP generation, and (3) The mechanism of reduction in Ca^{++}_i by FBP is consistent both with chelation of Ca^{++}_i by FBP or stimulation of mechanisms to regulate Ca^{++}_i. The details of these mechanisms, whether blockade of calcium entry, chelation of intracellular calcium, enhancement of Ca^{++} uptake into endoplasmic reticulum or mitochondria, or augmentation of ATP generation are currently under investigation.

References:

1. Crit. Care Med. 1988; 16: 954-63
2. Stroke 1990; 21: 606-13
3. J Cereb Blood Flow Metab. 1989; 9: 29-34
4. Cell Biochem and Function 1989; 7: 91-96

S27

Title: Does balloon dilatation angioplasty for coarctation of the aorta affect cerebrovascular circulation in children?

Authors: Bruno Bissonnette, Lee N Benson.
Affiliation: From the Department of Anaesthesia and Cardiology, The Hospital for Sick Children and the University of Toronto, Toronto, Ontario, Canada, M5G 1X8

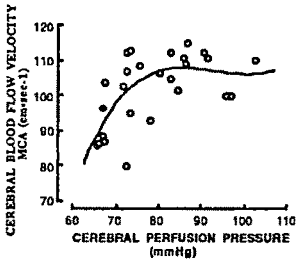
Introduction: Percutaneous balloon angioplasty for coarctation of the aorta, an alternative to surgery in young children, requires transient (30-45 sec) aortic occlusion distal to the carotid vessels. In this regard the impact of this technique on the cerebral circulation has not been evaluated.

Methods: With institutional approval and parental consent obtained, seven patients aged one to eight years old, ASA physical status I or II undergoing balloon dilatation were studied. General anesthesia was induced with thiopentone 5 mg/kg, fentanyl 5 µg/kg, diazepam 0.3 mg/kg. Neuromuscular relaxation was provided by vecuronium 0.2 mg/kg to facilitate tracheal intubation. Mechanical ventilation was maintained with 70% N2O in O2 (PaCO2 35-40 mmHg). No cerebral vasoactive agents were used. Ascending aortic mean arterial pressure (MAP) was measured continuously. Cerebral blood flow velocity (CBFV) in the middle cerebral artery was monitored with a transcranial Doppler (Transpect TCD, Medasonics). Central venous pressure (CVP) was obtained from the right atrium. Cerebral perfusion pressure (CPP) was calculated from MAP-CVP. Three CBFV and RI+ (cerebrovascular resistance index) readings were obtained during each inflation and deflation periods. Data are expressed as mean (± S.D.). A non-linear regression analysis was used to correlate the relationship between CBFV and CPP. Repeated-measures and SNK test for multiple comparisons was used for CBFV, MAP, HR, and CPP. A P<0.05 was accepted for statistical significance.

Results: Mean (±S.D.) age and weight were 51±12 mo and 23.4±13.5 kg, respectively. During each inflation MAP increased 42% (±8.2) above baseline while CBFV did not change. The RI+ decreased proportionally to the changes in the MAP. Cerebral autoregulation was maintained intact during each inflation (r2=0.18)(fig. 2).

Conclusion: During balloon angioplasty, cerebral autoregulation is preserved in spite of significant changes in systemic hemodynamics using this anesthetic technique. The transcranial Doppler is excellent to monitor the cerebral hemodynamic alterations during vascular interventions.

Fig. 1: Cerebral blood flow velocity is autoregulated when compared with cerebral perfusion pressure.



S28

Title: Does transcatheter closure of atrial septal defects affect cerebrovascular circulation in children?

Authors: Bruno Bissonnette, Lee N. Benson
Affiliation: From the Department of Anaesthesia and Cardiology, The Hospital for Sick Children and the University of Toronto, Toronto, Ontario, Canada, M5G 1X8

Introduction: Normal blood flow through brain tissue of the child averages 17-20 % of the total resting cardiac output.(1) Cerebral blood flow is autoregulated extremely well for pressure changes,(2) however, there is no clinical evidence that the brain has protective mechanism for acute alterations in cerebral blood volume (CBV). A finite blood volume is secluded in the pulmonary circulation with an atrial septal defect (ASD). After occlusion, this blood volume is acutely redistributed to the vascular bed. This study was designed to assess the effect of acute blood volume changes on the cerebrovascular circulation.

Methods: With institutional approval and parental consent obtained, five patients aged one to eight years old, ASA physical status I or II were studied during percutaneous transcatheter ASD closure. Induction of anaesthesia consisted of thiopentone 5 mg/kg, fentanyl 5 µg/kg, diazepam 0.3 mg/kg. Tracheal intubation was facilitated with vecuronium 0.2 mg/kg. Ventilation was maintained with 70% N2O in O2 (PaCO2 35-40 mmHg). No cerebral vasoactive agents were used. Mean arterial pressure (MAP) was measured. Cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA) was monitored (Transpect TCD, Medasonics, Fremont) . Central venous pressure (CVP) was obtained from the right atrium. Cerebral perfusion pressure (CPP) was calculated from MAP-CVP. The CBFV (Vmean) and RI+ (cerebrovascular resistance index) were obtained before ASD closure and for 15 min after closure. The CBV was calculated as the area under the curve (AUC).. Data are expressed as mean (± S.D.). Repeated-measures and the Student Newman-Keuls test were used for multiple comparisons. The AUC before and after closure was compared using paired Student T test. A P<0.05 was accepted as statistical significance.

Results: Mean (±S.D.) age and weight were 62±20 mo and 21±8 kg, respectively. Three out of five patients were female. .There was no changes in MAP, HR whereas CPP decreased after closure due to the increased in central venous pressure. The increase in the AUC was significant after closure of the ASD (P<0.05) The increase in Vmean was statistically significant after closure(p<0.05). Ri+ did not change.

Conclusion: While it is well known that the brain can maintain cerebral blood flow constant during changes in perfusion pressure, these observations may confirm the inability of the cerebral circulation to autoregulate transitory increases in CBV. This increase in CBV may results in an increase in intracranial pressure.

References:

1- Human Neuroanatomy, Williams & Wilkins, 1983
2- Br J Anaesth 48;719:1976

S29

Title: Umbrella occlusion of patent ductus arteriosus affects cerebrovascular circulation in anesthetized children?

Authors: Bruno Bissonnette^, Lee N. Benson*
Affiliation: Dept of ^Anaesthesia and *Cardiology, Hospital for Sick Children, Univ of Toronto, Ontario, Canada, M5G 1X8

Introduction: Ligation of patent ductus arteriosus (PDA) is one of the most common cardiac procedures performed in the pediatric patient.(1) It is suggested that the cerebral circulation may be at risk of intraventricular hemorrhage during ligation of PDA.(2) Transcatheter closure of PDA with umbrella device has become an non-surgical option. The hemodynamic effects of a PDA depend on the degree of left-to-right shunting. A finite blood volume is secluded in the pulmonary circulation with a PDA. After occlusion, this blood volume is acutely redistributed to the vascular bed. This study was designed to assess the effect of acute blood volume changes on the cerebrovascular circulation.

Methods: With institutional approval and parental consent obtained, ten patients aged one to eight years old, ASA physical status I or II were studied during percutaneous transcatheter PDA closure. Induction of anaesthesia consisted of thiopentone 5 mg/kg, fentanyl 5 µg/kg, diazepam 0.3 mg/kg. Tracheal intubation was facilitated with vecuronium 0.2 mg/kg. Ventilation was maintained with 70% N2O in O2 (PaCO2 35-40 mmHg). No cerebral vasoactive agents were used. Mean arterial pressure (MAP) was measured. Systolic (Vs) and diastolic (Vd) blood flow velocity in the middle cerebral artery (MCA) was monitored continuously (Transpect TCD, Medasonics, Fremont) . Central venous pressure (CVP) was obtained from the right atrium. Cerebral perfusion pressure (CPP) was calculated from MAP-CVP. The CBFV (Vmean) and RI+ (cerebrovascular resistance index) were obtained before PDA closure and for 15 min after closure. The CBV was calculated as the area under the curve (AUC).. Data are expressed as mean (± S.D.). Repeated-measures and the SNK test were used for multiple comparisons. The AUC before and after closure was compared using paired T test. P<0.05 was accepted as statistically significance.

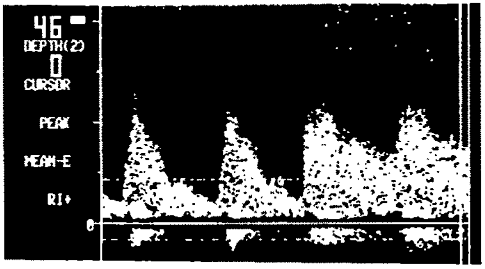
Results: Mean (±S.D.) age and weight were 30±22 mo and 13±5 kg, respectively. There was no changes in MAP, HR whereas CPP decreased after closure due to the increased in (CVP). Continuous recording during PDA closure showed an abrupt increase in Vd (P<0.05) whereas Vs did not change.(Fig. 1) The increase in the AUC was significant after closure of the PDA and last for 10 minutes (P<0.05) The increase in Vmean was statistically significant after closure (p<0.05).

Conclusion: The brain can maintain CBF constant during changes in CPP, however this may confirm the inability of the cerebral circulation to autoregulate acute changes in CBV. These major intracranial hemodynamic changes during PDA closure should be considered when selecting the anesthetic technique.

References:

1- Anesthesia for infants and children, C.V.Mosby Co., 1990
2- Acta Paediatric Scand 75;36:1986

Figure 1.



S30

TITLE: HYPERTENSION (HTA) AFTER CORONARY ARTERY GRAFTING (CABG): RANDOMISED COMPARISON OF NICARDIPINE, URAPIDIL AND SODIUM NITROPRUSSIDE

AUTHORS: Y.Blanloeil, M.D., D.Soulard,M.D., E.Meilhan, M.D., D.Portier, M.D., M.Videcoq, M.D.
AFFILIATION: D.A.R., Hôpital Laënnec, BP 1005, 440355 Nantes. FRANCE.

Introduction: Postoperative HTA has been reported in about 30 to 50% of patients after CABG. This study was designed to evaluate efficacy and safety of nicardipine (N), a new calcium antagonist of the dihydropyridine group (1) and urapidil (U), a postsynaptic alpha1 adrenoceptor blocker with additional agonist effect on cerebral 5HT1a receptors (2), in comparison to sodium nitroprusside (SNP), as antihypertensive agents in HTA following CABG.

Methods: With informed consent and approval of Nantes Ethics committee, 30 patients with ejection fraction >0.50 were randomly allocated to treatment of HTA when mean arterial pressure (MAP) was greater than 100 mmHg under fentanyl analgesia. Hemodynamic parameters, MAP, systolic (SAP), diastolic (DAP) arterial pressures, heart rate (HR), pulmonary wedge pressure (Pwp) and right atrial pressure (RAP) were recorded at T0 as baseline and 5,10,20,30,60 and120 min after initiation of treatment. Patients received either bolus of 1 mg N or 0.4 mg/kg U as required to obtain a MAP of 85±5 mmHg, then followed by continuous infusions. SNP was infused by increasing dose infusion by 0.5 µg/kg/min steps until MAP reached 85±5 mmHg . Infusions were stopped for MAP <70 mmHg. Statistics: Mean±SD; variance analysis and Scheffe test.

Results: Mean boluses doses were 0.4 mg/kg for U and 3.66±2 mg/kg for N. Mean maintenance doses were 70±24 (U), 0.95±0.45 (N) and 1±1.2 (SNP) µg/kg/min infused respectively during 130±78, 200±58 and 204±65 min. Hemodynamic parameters at T0, 10, 30, 60 and 120 min are summarized on the Table. MAP was lower with U than SNP at 5, 60 and 120 min (p<0.05). Hemodynamic profile of SAP and DAP variations were similar to MAP evolution for all drugs. Pwp decrease only with SNP (p<0.05). HR was higher with SNP than U at T30, 60 and 120 (p<0.05). No cardiac incident (ischemia, infarction or arrythmias) were recorded in any group.

Conclusion: Absence of HR increase with U over N and SNP is an advantage in patients with coronary artery disease. However, because of its long half-live of elimination, U may be used by repeated boluses to avoid risk of coronary underperfusion when prolonged infusion leads to hypotension.

References:

1. J Cardiothorac Anesth 3: 344-55, 1989.
2. Br J Anesth 64: 493-7, 1990.

		T0	T10	T30	T60	T120
MAP mmHg	U	110±7	93±18 a	83±10 c	72±10 c	74±7 c
	SNP	119±18	108±28	86±8 a	87±13 b	86±9 b
	N	114±10	90±13 c	81±14 c	80±10 c	76±11 c
HR b/min	U	77±22	83±22	83±21	83±18	86±15
	SNP	89±13	99±16	106±18 b	106±18 b	107±10 b
	N	85±9	87±14	96±12	99±15 b	99±11 a
Pwp mmHg	U	8.5±2.5	6.7±3.2	6.3±2.4	6±2.7	6.2±2.5
	SNP	9.9±2.4	8.2±2.5	7±1.9	6.4±3.2 a	7.1±2.3
	N	10.7±6	8±3.2	8.2±2.4	7.7±2.8	7.3±3.4

Scheffe intra-group, significance from T0: a) p<0.05, b) p<0.01 c) p<0.001.

S31

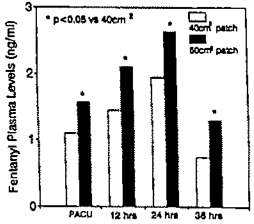
Title: TRANSDERMAL FENTANYL: POSTOPERATIVE ANALGESIA AND PLASMA LEVELS AFTER MAJOR ORTHOPEDIC SURGERY

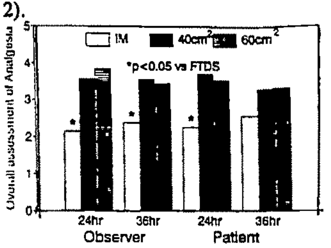
Authors: TF Boerner MD, R Bartkowski MD PhD, M Torjman MEd, J Lessin RN, A Marr CRNA
Affiliation: Department of Anesthesiology, Jefferson Medical College, Philadelphia, PA 19107

Introduction: Transdermal fentanyl (FTDS) provides effective analgesia[1] and steady plasma fentanyl levels[2] following abdominal surgery. We evaluated the abilities of two formulations of FTDS to provide adequate plasma fentanyl levels and postoperative analgesia following major, painful orthopedic surgery. We compared both FTDS patches with IM morphine.

Methods: Sixty-one ASA PS I-II patients scheduled for elective spine or reconstructive knee surgeries consented to this IRB approved study. All patients were premedicated with 10 mg diazepam po. Prior to induction of anesthesia, patches (40cm^2, 60cm^2 fentanyl or placebo) were placed on the patient's chest wall or back and remained in place for up to 24 hours. Strength was allocated in a randomized, double-blind fashion. Prior to incision, all patients received 5μg/kg fentanyl IV. No more narcotics were administered during surgery. Anesthesia consisted of thiopental, muscle relaxant, and isoflurane as needed. Postoperatively, patients were monitored for 24 hrs or until "rescue" IM analgesia was required. When awake, patients rated pain and comfort and were offered IM injections every 6 hrs. The morphine group received IM injections of morphine 150μg/kg, while the FTDS groups received placebo. The patient and monitor independently judged overall pain management at the conclusion of the study. Venous blood was collected at 12, 24 and 36 hours after patch application and analyzed for fentanyl concentration. Data was analyzed by ANOVA with repeated measures and Kruskal-Wallis tests with $p<0.05$ significant.

Results: There were no differences between the three groups in age, weight, sex or ASA status. Nine of 19 patients receiving IM morphine withdrew from the study because of pain, but only 2 of 21 and 4 of 21 patients in the 40cm^2 and 60cm^2 patch groups withdrew. In the in the 60cm^2 group, 2 patients' patches were removed due to respiratory depression and one due to nausea. No patch in the 40cm^2 group was removed due to side effects. Plasma fentanyl levels were significantly greater in the 60cm^2 FTDS group at all tested times postoperatively (graph 1). There were significant differences between IM morphine and the two FTDS groups both in observer and patient assessment of analgesia after 24 hours. The observer also judged the FTDS patients to be significantly more comfortable at 36 hours (graph 2).





Discussion: Analgesia after major orthopedic surgery is significantly better using either FTDS patch formulation compared with this IM morphine regimen. The evaluation of analgesia was not different between the two FTDS groups. Plasma fentanyl levels were consistently higher in the 60cm^2 group, and the only patients with severe narcotic side effects were in this group. In summary, 40cm^2 FTDS is a promising alternative to IM morphine for major orthopedic surgery.

Reference: 1. Pain 40(1990) p.21-28 2. Pain 37(1989) p.15-21

S32

TITLE: ISOFLURANE AND HALOTHANE DECREASE ACETYLCHOLINE INDUCED EDRF DEPENDENT RELAXATION OF RABBIT AORTA ARTERY

Authors: Bruce Bollen.M.D., James Bates, M.D., Gilbert Aldape, M.D., and Ray Davies
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Introduction:

Anesthetic agents have been reported to cause endothelial dependent relaxation, cause relaxation not dependent on endothelial mechanisms, and to inhibit EDRF induced relaxation of arterial segments. This study examined the dose dependent effect of halothane and isoflurane on acetylcholine induced (endothelial dependent) relaxation of rabbit aortic segments previously contracted with phenylephrine.

Methods:

Male New Zealand rabbits weighing 4-7 pounds were euthanized with pentobarbital. The thoracic aorta was removed, placed in Krebs solution and cut into ring segments 3-4 mm long. Ring segments were suspended in 25 ml organ chambers using Grass strain gauges to record tension.

Optimal resting tension was determined. Arterial segments were contracted with phenylephrine 3x 10^{-7}M. Following stabilization of contraction, an acetylcholine (Ach) dose response with (1) protocol 1: $3x10^{-8}$, $1x10^{-7}$, and $3x10^{-7}$M or (2) protocol 2: $1x10^{-8}$, $1x10^{-7}$ $1x10^{-6}$, $3x10^{-6}$, and $1x10^{-5}$M was performed on each vessel. ACh dose response was repeated three times per vessel: (1) initially without anesthetic present, (2) with anesthetic present, and (3) repeated again without anesthetic present. Concentrations of isoflurane and halothane studied were 0.5, 1.0, 2.0, and 3.0% for protocol 1, and 1.0 and 3.0% for protocol 2. Individual arterial segments were exposed to only one anesthetic concentration.

A total of 38 rabbits and 255 vessels were studied. A repeated measures ANOVA was used to analyze data. $P < 0.05$ was considered significant.

Results: The ACh relaxation dose response curves for protocol 1 were significantly decreased in the presence of isoflurane and halothane at 0.5, 1.0, 2.0 and 3.0%. The ACh dose response curves for protocol 2 in presence of 1.0 and 3.0% halothane and isoflurane were shifted to the right of controls, and their maximum relaxation was significantly less than that seen in absence of anesthetic.

Discussion:

ACh induced endothelial dependent relaxation of a phenylephrine contraction in rabbit thoracic aorta is depressed by isoflurane and halothane in a dose dependent manner. The depression involved both changes in ED_{50} of ACh and depression of the maximum response to ACh. The etiology of this depression remains to be elucidated.

References:
1. Anesthesiology 1987; 66:748-752
2. Anesthesiology, 1988; 68:31-37
3. Anesthesiology 1990; 73:100-108

S33

Title : PROPOFOL DOES POSSESS ANTIEMETIC PROPERTIES

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Recent studies have constantly shown that general anesthesia conducted with propofol is associated with less nausea and vomiting during the early postoperative period than with any other anesthetics (1,2). Some authors have suggested that propofol might have direct antiemetic properties (3). The aim of the present study was to investigate the possible antiemetic properties of propofol.

After informed consent and institutional approval, 52 patients (ASA I-II) scheduled for minor gynecologic, digestive or orthopedic surgery were included in the study, which was conducted in a randomized double blind fashion. As soon as nausea or vomiting occurred in the recovery room, the patient received either a subhypnotic dose of propofol (10 mg i.v. = 1 ml) or 1 ml of placebo (Intralipid ^{R}). If there was no response a second dose was administered one minute later. If the patient was still nauseous or vomiting one more minute later, the patient treatment was considered to have failed. Study duration was 30 minutes. The level of sedation and the appearance of side effects were closely monitored.

The two groups were similar with regard to age, sex and type of surgical procedure (Table 1). Anesthetic technique was similar for all patients : thiopental, enflurane, fentanyl and vecuronium as necessary. The rate of success in treating nausea and vomiting was significantly higher with propofol as compared to placebo : 81 % versus 35 % respectively ($p < 0.05$). On the other hand, the rate of recurrence of nausea or vomiting within the first 30 minutes was similar in both groups (28 % versus 22 % respectively). The level of sedation increased in 33 % of the propofol patients and in 44 % of the placebo group. Level of pain, mean blood pressure or heart rate were unchanged. Pain on injection was noted in 7.6 % (placebo : none) and dizziness in 3.6 % (placebo : none) in the propofol group (n.s.). Euphoria or dysphoria were not observed in neither groups.

Following minor gynecologic, digestive or orthopedic surgery in ASA I or II patients, propofol was significantly more effective in treating postoperative nausea or vomiting than placebo. Side effects associated with propofol were minor and rare. We concluded that propofol does possess specific antiemetic properties whose mode of action remains to be elucidated.

Table 1 :

	Propofol	Placebo	
Age	42 ± 4	36 ± 3	n.s.
Male/Female	9 / 17	5 / 21	n.s.
Surgical procedure :			
minor gynecologic	15	18	
minor digestive	9	7	n.s.
minor orthopedic	2	1	

References :
1. Anesthesiology 71:63-71, 1988; 2. Anaesthesia 43:239-240, 1988; 3. Br J Anaesth 59:654-655 P, 1987.

S34

Title: FREE POLYMERISED HEMOGLOBIN VS HYDROXY-ETHYLSTARCH IN RESUSCITATION OF BLED DOGS

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Introduction: Instantaneous restoration of (micro-)circulation and (tissue-) oxygenation are essential for the outcome of hypovolaemic shock. Shortage of blood-donors and the potential infections limit the use of blood-transfusions. In this study a comparison between polymerised bovine hemoglobin (Hemopure I, B. Braun Melsungen) and hydroxy-ethylstarch in a hypovolemic shock model in dogs was done based on hemodynamic changes on days 1 and 7, and metabolic changes on days 1, 2, 3 and 7.
Methods: Eighteen anesthetized dogs were hemorrhaged and maintained at a systolic arterial pressure of 40 mm Hg for 30 minutes. Six dogs functioned as a control group (CTR group) and received their own shed blood, six dogs were infused with hydroxyethylstarch (6%, MW 200.000, in NaCl 0.9%,HES group) and six dogs received Hemopure I (hemoglobin content: 11 ± 2 g/100ml., osmolarity: 250 ± 40 mosm/kg., HEM group), both in an equal amount to the shed blood. Statistical analysis was performed using Student's t test. $P \leq 0,05$ was considered significant.
Results: table 1. In the HES group a 258% increase in cardiac output (with a concomitant increase in heart rate and stroke volume) compensated for the lowered arterial oxygen content (CaO_2), whereas cardiac output (CO) and heart rate in CTR and HEM groups returned to, or rose slightly above, baseline value. After resuscitation, hematocrit fell to 56-62% of base line values in the HEM and the HES groups, however normal values were obtained at day 1. Diuresis was significantly enhanced during the first 24 hours in the HEM group. During the following week no detoriation of the kidney function could be found.
Discussion: Early recovery from hypovolemic shock, particularly in regard to oxygen transport and delivery, in the HEM group seemed to be comparable to the CTR group, without the strenuous effects on the cardiovascular system seen with HES infusion.

	group	control	shock	resuscitation	day 7
heart rate (bpm)	CTR	57 ± 9	209 ± 39	75 ± 23	58 ± 9
	HES	74 ± 32	186 ± 14	107 ± 19^{ac}	66 ± 7
	HEM	60 ± 8	188 ± 23	65 ± 13	74 ± 20
mean CO. (ml/min/kg)	CTR	95 ±23	71 ±7	125. ±21	95 ±11
	HES	85 ±24	56 ±8^{a}	219 ±96^{ac}	116 ±22
	HEM	92 ±21	62 ±9	100 ±18	137 ±65
DO2 (ml/min/kg)	CTR	16. ±5	12 ±1	21 ±5	13 ±2
	HES	14 ±3	10 ±2	26 ±14	17 ±3
	HEM	18 ±4	12 ±2	16 ±3	18 ±9
VO2 (ml/min/kg)	CTR	4.2 ±0.8	5.7 ±1.1	4.8 ±0.6	3.4 ±1.0
	HES	3.4 ±0.7	4.8 ±2.0	6.5 ±3.3	4.4 ±1.1
	HEM	3 0±0.4^{b}	4.6 ±0.8	3.9 ±0.7	5.7 ±2.9

table 1 All results are represented as mean ± S.D.
[a] significant difference between CTR and HES.
[b] significant difference between CTR and HEM.
[c] significant difference between HES and HEM.

S35

Title: CONTROVERSIAL PRACTICES AND HABITS AMONG ANESTHESIOLOGISTS: A SURVEY

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Introduction: Research and changing anesthetic techniques may render common practices outmoded and inappropriate, even dangerous. We observed that some anesthesiologists continue to use various anesthetic techniques despite research evidence that supports alternative methods. A questionnaire was devised to assess the utilization of some of these procedures among anesthesiologists in Florida. Demographic variables were evaluated to determine possible relationships to these practices. We sought to determine the frequency with which anesthesiologists practice inappropriate or outdated techniques.

Methods: A survey was mailed to anesthesiologists listed in the directory of the Florida Society of Anesthesiologists. The survey requested the respondent's age, sex, anesthesia training, location and type of practice, and hospital size. Questions concerning practice habits included use of (1) preoperative antisialagogues, (2) IM injections for preoperative sedation, (3) pulse oximetry, (4) capnography, (5) oxygen in monitored anesthesia care, (6) halothane in adults, (7) succinylcholine in patients with chronic renal failure, (8) reversal of intermediate duration neuromuscular blockers, (9) adjunct narcotics with inhalational agents, (10) Allen's test, (11) mask anesthetics, (12) routine application of oxygen in the PACU, (13) rapid sequence anesthetic induction of morbidly obese patients, (14) spinal anesthesia in outpatients, (15) peripheral nerve blocks, and (16) curare prior to administration of succinylcholine. Questions were answered on a scale based on respondents' estimated use of each item (%): 0=never, 25=seldom, 50=occasionally, 75=frequently, and 100=always.

Results: Of 1,322 questionnaires mailed, 493 (37%) were returned. The use of pulse oximetry and capnography approached 100%. Partial results from the remainder of the survey are summarized in the table.

	Frequency of Use (%)				
Question Topic	0	25	50	75	100
Antisialagogue	30	27	11	20	12
IM premedicants	37	28	12	16	7
Halothane	77	21	1	0.8	0
Succinylcholine	43	28	19	7	3
Postoperative O_2	2	4	6	15	73
Outpatient spinal	32	49	14	3	2
Defasciculation	11	11	10	23	45

Discussion: The survey revealed that common anesthetic practice frequently varies from the current standard of care. For example, preoperative antisialagogues and IM injections are still administered, despite the use of modern volatile agents and the availability of oral premedicants. Investigators in the early seventies demonstrated that succinylcholine does not cause an abnormal increase in serum potassium.[1] It is well known that a defasciculating dose of curare somewhat inhibits the action of succinylcholine and is of little value in some patient groups, and the use of halothane in adults may be indicated, eg, inhalation induction in a patient with bronchospasm. The frequency of various practices and habits among Florida anesthesiologists were polled. Results confirmed that outmoded and inappropriate techniques persist in current practice. However, an encouraging note was the almost universal use of pulse oximetry and capnography.

References: 1. Anesthesiology 36:138-141, 1972

S36

TITLE: PROPOFOL INFUSION: DOSE-RESPONSE FOR CT SCANS IN CHILDREN

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A Rodarte MD, D Frankville MD

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INTRODUCTION: Many different anesthetic agents and techniques have been used in children to provide anesthesia for radiologic imaging procedures. The ideal technique should be safe and reliable, have rapid onset with minimal respiratory depression and need for airway support, provide a motionless patient, and still allow rapid awakening. The purpose of this study was to evaluated intravenous propofol as an anesthetic for computerized tomography in children when given by continuous infusion, and to determine the minimum effective infusion dose.

METHODS: After IRB approval and parental informed consent, we studied 25 children, ASA physical status 1 or 2, with a mean age of 3.4 years (range 8 mo-7 yrs), and a mean weight of 15.2 kg (range 7-23 kg). Propofol boluses and infusions were given via a Baxter infusion pump (model AS20GH-2). The minimum propofol dose necessary to induce unconsciousness was given by administering an initial dose of 1.5 mg/kg, followed by additional doses of 0.5 mg/kg every 30 seconds until lose of consciousness ensued. An escalating dosage schedule was then used to determine the minimum effective continuous propofol infusion dose necessary to maintain unconsciousness during the CT scan. We empirically started with a very low infusion dose of 25 mcg/kg/min. If arousal or movement occurred in 2 patients at a given infusion dose, that dose would be considered a failure and subsequent patients would then receive the next higher maintenance infusion (50,75,100 mcg/kg/min) until 5 consecutive patients completed the scan without movement at a given dose. Patients were monitored by pulse oximetry and capnography. The capnogram was obtained by using a nasal airflow probe, and monitored for episodes of apnea. Recovery from anesthesia was assessed by recording the time interval to eye opening immediately after termination of the propofol infusion, as well as the time interval until fully awake.

RESULTS: The mean scan duration was 30 minutes(range 17-58 min). Loss of consciousness was induced with a mean total propofol dose of 2.8 mg/kg(range 2.0-5.0 mg/kg). At the initial propofol infusion rate of 25 mcg/kg/min, completion of the scan without movement or arousal occurred in 5 consecutive patients. In order to determine if any infusion was necessary to maintain unconsciousness, 3 subsequent patients received no infusion following induction of anesthesia, 2 of which moved before the completion of the scan (11 and 13 min). Fifteen additional patients were studied at 25 mcg/kg/min, 13 of whom completed the scan without movement. Two patients, however, exhibited movement and arousal during the scan when the head was repositioned from neutral to hyperextension for coronal images of the temporal bones. Similarly, head repositioning resulted in patient arousal in 2 patients receiving 50 mcg/kg/min. The initial oxygen saturation (SaO2) following induction was 97% (range 93-100%). The lowest SaO2 at any time during the case averaged 95% (range 80-99%). Only 1 patient had a saturation less than 90%, which was associated with a period of transient apnea immediately following bolus induction, but quickly recovered without the need for intervention. No patient required airway support or supplemental oxygen at any time. All patients who received the 25 mcg/kg/min maintenance infusion, and required no position change, remained asleep for the duration of the scan. Following termination of the propofol infusion, 72% of these patients were awake (eyes open) immediately. The mean time to eye opening was 1.0 min (range 0-8min), and the mean time until fully awake was 2.5 min (range 0.5-9.0 min). No patient required postanesthesia care unit (PACU) admission.

CONCLUSION: Following induction of anesthesia with intravenous propofol, an infusion of 25 mcg/kg/min was the minimum effective dose necessary to maintain a motionless patient for computerized tomography. This technique was reliable, allowed continued spontaneous respiration, and was associated with a very rapid and complete recovery eliminating the need for PACU admission. However, the depth of anesthesia at 25 and 50 mcg/kg/min proved inadequate for patients head repositioning. For scans involving patient repositioning, either a higher propofol infusion rate or supplemental propofol boluses may be indicated prior to repositioning.

S37

TITLE: COMPARISON OF SPINAL 8% TETRACAINE TO 0.75% BUPIVACAINE IN NEWBORN RABBITS

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AFFILIATION: Departments of Anesthesia, Children's National Medical Center and Uniformed Services University of the Health Sciences

Introduction: Spinal anesthesia in the newborn pediatric patient has enjoyed an increase in popularity over the last decade(1,2). Although clinically no problems have been noted nothing is known about possible histopathology in the newborn spinal cord. This study compares the effects of a known injurious concentration of tetracaine to a clinically relevant concentration of bupivacaine.

Methods: After institutional approval, four groups of newborn New Zealand white rabbits were studied. The groups were divided into: 8% tetracaine, 0.75% bupivacaine, normal saline and controls. A low amperage nerve stimulator was used to identify the correct location, a modification of Ready's method(3). Following tail twitch stimulation with a 25 gauge needle, the appropriate solution was injected at the S1-S2 interspace. Four animals were sacrificed in each group at 2,7, & 30 days. Spinal cords were fixed and then prepared for both electron and light microscopic evaluation by a blinded neuropathologist.

Results: Recovery was complete clinically within one hour in all groups. The 8% tetracaine group showed a progression of histopathologic changes. The peak changes were at 7 days post injection. Moderate numbers of dilated myelin sheaths were seen with their component axons swollen and fragmented. At 30 days there was no difference between 8% tetracaine, normal saline and controls. Specimens from animals injected with 0.75% bupivacaine injectates showed no significant histopathologic changes as seen in the 8% tetracaine group at any time.

Discussion: 8% tetracaine, a known toxicologic concentration, caused significant histopathologic changes in the newborn spinal cord. At 30 days out, no changes are noted. 0.75% bupivacaine showed no significant changes in any of the groups. Clinically relevant concentrations of bupivacaine appear to be safe and cause no long term histopathologic changes in the developing spinal cord.

REFERENCES:
1. Anesth Analg 63:359, 1984
2. Anesthesiology 72:838, 1990
3. Anesthesiology 63:364-370, 1985

S38

Title: MECHANICAL VENTILATION IN THE PRONE POSITION FOR ACUTE RESPIRATORY FAILURE AFTER CARDIAC SURGERY

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INTRODUCTION: Pulmonary gas exchange is frequently impaired after cardiac surgery. Recent studies have demonstrated collaps of dependent lung regions secondary to anesthesia and muscle paralysis (1). These alterations of lung structure may persist postoperatively and contribute to the poor respiratory function. Thus in this study lung function and structural lung changes after coronary artery bypass grafting (CABG) were determined. In addition treatment of respiratory failure by ventilation in the prone position was compared with conventional mechanical ventilation.

METHODS: After IRB approval and informed consent had been obtained 8 patients were studied. The inclusion criteria were: Stable hemodynamics, absence of volume overload, adequate renal function, an inspired oxygen fraction (FiO_2) $\geq$ 0.5 to maintain a PaO_2 of > 75 mmHg, an alveolar-arterial PO_2 difference ($P_{A\text{-}a}O_2$) $\geq$ 200mmHg and total venous admixture (Q_s/Q_T)>15% despite conventional ventilation with PEEP of 5 cmH_2O. Patients with preexisting pulmonary disease were excluded. Anesthesia was induced and maintained by weight related doses of midazolam, fentanyl, pancuronium and enflurane (0.5-1.0 MAC). In patients fulfilling the inclusion criteria postoperatively a cardiopulmonary status and chest CT-scans were obtained. Lung structure was analysed by densitometry, relating attenuation values to tissue density. Lung parenchyma presenting attenuation values in the range of -300 to +20 Hounsfield units was defined as atelectasis/dystelectasis. Then patients were placed in the prone position and ventilated with a PEEP of 7.5 cmH_2O and an inspiratory-expiratory ratio of 2. A further cardiopulmonary status was obtained after 60 min. Student's t test was used to test for between group differences and correlation was tested by linear regression analysis. P< 0.05 was considered significant.

RESULTS: Hemodynamic data and pulmonary status are shown during ventilation in the supine and the prone position.

		Conventional mechanical ventilation in the supine position	Mechanical ventilation in the prone position	
HR	(beats/min)	95±18	99±22	
MAP	(mmHg)	79±4	86±7	
MPAP	(mmHg)	19±5	17±5	
POP	(mmHg)	9±2	11±4	
CI	(l/min/m2)	3.2±0.5	3.3±0.5	
SVR	(dyn s cm5)	975±197	968±253	
PVR	(dyn s cm5)	131±24	109±34*	(p<0,05)
PaO2	(mmHg)	79±5	99±25	
PaCO2	(mmHg)	40±4	41±3	
PA-aO2	(mmHg)	342±141	129±32*	(p<0,02)
FiO2		0.67±0.18	0.39±0.05*	(p<0,006)
VO2	(ml/min)	241±69	253±56	
DO2	(ml/min)	876±142	995±175	
QS/QT	(%)	33.3±7.8	16.8±2.5*	(p<0.002)

All patients that met the inclusion criteria revealed considerable amounts (21.3+16.6% of total lung volume) of crest shaped bilateral densities in dependent lung regions. The magnitude of the atelectatic areas correlated well with Q_s/Q_T (r=0.8). Hemodynamic conditions were not altered by mechanical ventilation in the prone position. However gas exchange improved significantly. Q_s/Q_T and $P_{A\text{-}a}O_2$ decreased and as a result FiO_2 could be reduced from 0.67 to 0.39.

CONCLUSION: Respiratory insufficiency after CABG is associated with atelectasis in dependent lung regions. Conventional ventilatory treatment was less effective in these cases, however gas exchange was significantly improved by inversed ratio ventilation in the prone position. Recently Gattinoni showed that ventilation in the prone position is little effective in ARDS (2). The good results observed in the present study further underline the importance of atelectasis formation during cardiac surgery.

Ref: 1) Hedenstierna G. Acta Anaesthesiol Scand 30:183-91,1986
2) Gattinoni L. Anesthesiology 74:15-23,1991

S39

TITLE: COMPARISON OF IV-PCA VS EPIDURAL-PCA FOLLOWING MAJOR VASCULAR SURGERY

AUTHORS: J. Bustamante, M.D., Y. Sawaki, M.D., P. F. White, Ph.D., M.D.
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Epidural analgesia has been reported to provide improved pain relief compared to standard parenteral techniques following major intra-abdominal procedures. We designed a study to compare the efficacy of the epidural and intravenous routes of opioid administration when using a patient-controlled analgesia (PCA) delivery system.

48 consenting patients undergoing abdominal aortic aneurysm resection or aortobifemoral bypass grafting procedures were randomly assigned to receive either intravenous (n=23) or epidural (n=25) morphine from a PCA device for postoperative pain relief. Patients in the epidural group received preservative-free morphine 65 µg/kg epidural prior to aortic cross clamping. Postoperatively, morphine was infused either intravenously (IV-PCA:1.5 mg/h) or epidurally (EPI-PCA: 5 mg/h in 2.5 ml) for the first 12h after surgery. Supplemental bolus doses of morphine equal to 2 mg (IV-PCA) or 1.5 mg (EPI-PCA) could be administered "on demand" throughout the 72h study period using an Abbott Provider 5500 system. Patients completed daily analog scales for pain, anxiety, drowsiness, nausea, and itching. Morphine dosage requirements, recovery times and side effects were also recorded. Pulmonary function tests (PFTs), including forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV1), were performed on 8 patients in each group preoperatively and on POD #1, #3 and #6 using a Respiradyne monitor. Data were analyzed by ANOVA, with $p<0.05$ considered statistically significant.

Compared to IV-PCA, morphine requirements were significantly lower in the EPI-PCA group (table). However, recovery of bowel and bladder function, ability to tolerate a liquid diet, and times to ambulation and discharge were similar in both groups. Pain scores were significantly lower in the EPI-PCA (vs IV-PCA) group on POD #1 only. Nausea, drowsiness and anxiety scores were similar in both groups. Itching scores were significantly higher in the EPI-PCA group. PFTs revealed a greater decrease in the FVC on POD #1 in the IV-PCA group, however, there were no other differences in the PFT values between the two groups.

In conclusion, EPI-PCA required significantly less morphine than IV-PCA following major vascular surgery. However, this opioid-sparing effect did not result in a decrease in opioid-related side effects or improve outcome.

Morphine dosage requirements (mg/8h) (Means ± S.D.)

	POD #1	POD #2	POD #3
IV-PCA	9.6±7.7	9.1±8.8	9.9±9.4
EPI-PCA	3.2±2.7*	3.0±2.2*	2.9±3.4*

* Significantly different from IV-PCA, $p<0.05$

S40

TITLE: ASSESSMENT OF RESIDUAL BLOCKADE BY 50 Hz AND 100 Hz TETANY: A COMPARISON WITH TRAIN-OF-FOUR RATIO

AUTHORS: P.R. Causton, B.S., R.L. Lennon, D.O., and K.A. Jones, M.D.
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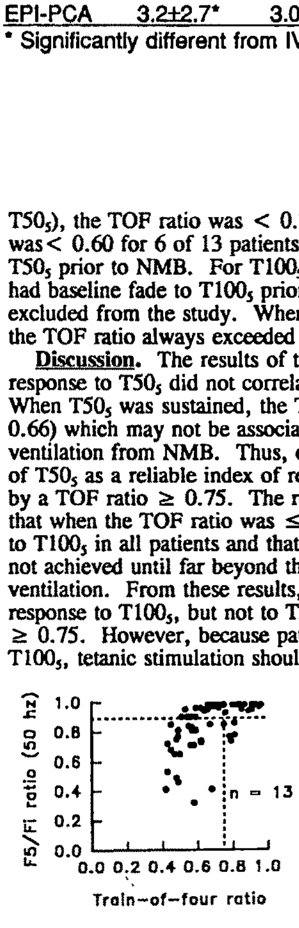
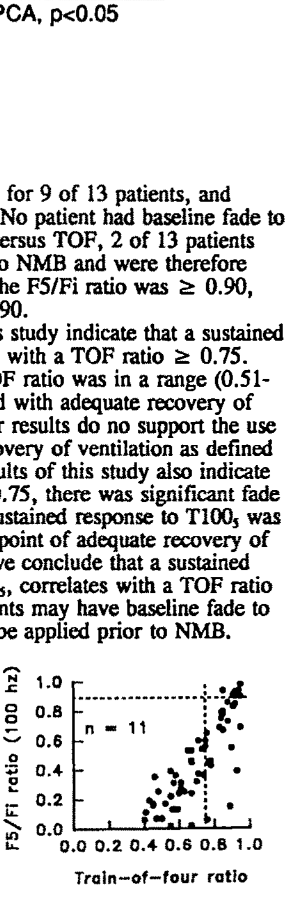
Introduction. Anesthesiologists have frequently interpreted a sustained muscle response evoked by 50 Hz and 100 Hz tetany for 5 s (T50$_5$ and T100$_5$) as adequate clinical recovery of neuromuscular function. Since a train-of-four (TOF) ratio ≥ 0.75 indicates adequate recovery of ventilation from neuromuscular blockade (NMB), we hypothesized that if T50$_5$ or T100$_5$ is sustained, the TOF ratio will be ≥ 0.75. The purpose of this study was to test this hypothesis during spontaneous recovery from vecuronium NMB.

Methods. Following IRB approval and informed consent, 13 ASA 1 and 2 adult patients undergoing isoflurane anesthesia for elective orthopedic procedures were studied. The ulnar nerve was supramaximally stimulated at the wrist with a peripheral nerve stimulator. During spontaneous recovery from vecuronium NMB, the force of the thumb contractions evoked by T50$_5$, T100$_5$, and TOF stimulation were measured with a mechanomyograph at TOF ratios from 0.4 to 1.0. The degree of fade to T50$_5$ and T100$_5$ were expressed as the ratio of the force at 5 s to the initial force (i.e., F5/Fi ratio). An F5/Fi ratio ≥ 0.90 was considered sustained force.

Results. Comparisons between the T50$_5$ and T100$_5$ F5/Fi ratios with the TOF ratios are shown in the figures. For T50$_5$ versus TOF, when the F5/Fi ratio was ≥ 0.90 (i.e., no fade to T50$_5$), the TOF ratio was < 0.75 for 9 of 13 patients, and was < 0.60 for 6 of 13 patients. No patient had baseline fade to T50$_5$ prior to NMB. For T100$_5$ versus TOF, 2 of 13 patients had baseline fade to T100$_5$ prior to NMB and were therefore excluded from the study. When the F5/Fi ratio was ≥ 0.90, the TOF ratio always exceeded 0.90.

Discussion. The results of this study indicate that a sustained response to T50$_5$ did not correlate with a TOF ratio ≥ 0.75. When T50$_5$ was sustained, the TOF ratio was in a range (0.51-0.66) which may not be associated with adequate recovery of ventilation from NMB. Thus, our results do no support the use of T50$_5$ as a reliable index of recovery of ventilation as defined by a TOF ratio ≥ 0.75. The results of this study also indicate that when the TOF ratio was ≤ 0.75, there was significant fade to T100$_5$ in all patients and that sustained response to T100$_5$ was not achieved until far beyond the point of adequate recovery of ventilation. From these results, we conclude that a sustained response to T100$_5$, but not to T50$_5$, correlates with a TOF ratio ≥ 0.75. However, because patients may have baseline fade to T100$_5$, tetanic stimulation should be applied prior to NMB.





S41

TITLE: MONITORING OF INTRACRANIAL PRESSURE (ICP) DURING LIVER TRANSPLANTATION

AUTHORS: JW Chapin, MD, JB Morgan, MD, BW Shaw Jr, MD, GL Becker, MD, R Pohorecki, MD

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Fulminant hepatic failure (FHF) is coagulopathy and encephalopathy in patients with liver disease < 8 weeks in duration. We monitored ICP and CPP in patients undergoing liver transplantation for FHF.

Methods Ladd monitors were placed for perioperative ICP measurement in 18 consecutive patients with FHF and grade III or IV coma. Cerebral perfusion and mean arterial pressures (CPP, MAP) and ICP were recorded at the stages of surgery shown in Fig. 1. Hyperventilation (P_{aCO_2} = 25-30 mmHg), head elevation and mannitol or thiopental infusion were used to lower ICP, and phenylephrine, inotropes and volume to raise MAP.

Results Fig. 1 shows that pressures changed significantly (P<.05 by ANOVA) only during reperfusion: MAP decreased, ICP increased and CPP decreased. Transient increases in ICP were seen with head turning, Trendelenberg, caval clamping and volume replacement.

Discussion In this study, monitoring of ICP during liver transplantation furnished valuable data concerning the impact of intraoperative events on cerebral perfusion in patients with FHF and severe encephalopathy. More work is needed to determine if preventing sustained increases in ICP and keeping CPP > 50 mmHg improve neurologic outcome.[1,2]

References 1. Gut 21:866, 1980.
2. Seminars Liver Dis 9:189, 1989.

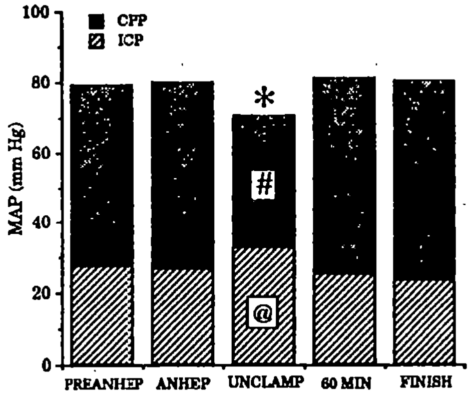

Figure 1 Mean MAP, ICP and CPP during liver transplantation (N= 21 transplants). *MAP, #ICP and @CPP values at unclamping differ from those in other stages.

S42

TITLE: THE DYSRHYTHMIC THRESHOLD FOR EPINEPHRINE DURING SEVOFLURANE ANESTHESIA IN HUMANS

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Introduction: Sevoflurane is an expermental inhaled anesthetic with some advantages over currently used inhaled anesthetics. The current study evaluated the dysrhythmic threshold of epinephrine in humans anethesized with sevoflurane versus isoflurane.

Methods: Twenty eight ASA class I or II patients undergoing transsphenoidal hypophysectomy were studied (after informed consent and approval by the Committee on Human Research, University of CA, San Francisco). After premedication with up to 2mg of midazolam and 100ug of fentanyl, anesthesia was induced with sevoflurane or isoflurane (assigned randomly), and endotrachael intubation was facilitated with vecuronium 0.15mg/kg. Anesthesia was maintained between 1.0-1.3 MAC and ventilation was adjusted to maintain normocarbia. Lead II of the ECG was continuously monitored. Patients received 1:50,000, 1:75,000 or 1:100,000 epinephrine in saline injected submucosally over 2-3 minutes to a total volume determined by the surgeon, who was blinded with respect to anesthetic agent and epinephrine concentration. The dysrhythmic threshold was defined as the epinephrine dose that produced 3 or more PVCs within the 10 minutes following the injection.

Results: The isoflurane and sevoflurane groups were comparable with respect to mean age, height, weight and sex distribution. Fourteen patients received sevoflurane with epinephrine doses ranging from 3.9 to 11.3ug/kg. Three positive responses occurred at 5.0, 7.1, and 7.9ug/kg. The fourteen patients randomized to isoflurane anesthesia received epinephrine doses ranging from 4.0 to 9.8ug/kg. There were three positive responses in this group, at doses of 4.0, 7.8, and 8.0ug/kg.

Discussion: These preliminary data suggest that sevoflurane and isoflurane do not differ in their lack of sensitizing of the myocardium to exogenously administered epinephrine(fig 1). Doses less than 5.0ug/kg did not provoke arrhythmias in the presence of sevoflurane. This value is comparable to animal data and is significantly less than the arrhythmogenic dose in the presence of halothane (3). The epinephrine dose producing a positive response for 50% of patients anesthetized with sevoflurane requires continuing investigation. However, the current data indicates that it will not be significantly less than that epinephrine dose necessary to initiate arrhythmias in patients anesthetized with isoflurane.

1. Anesthesia and Analagesia 55:709-712, 1976.

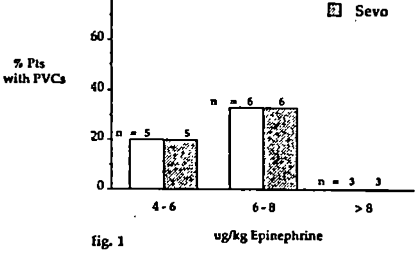

fig. 1

S43

Title: REAL-TIME ST SEGMENT ANALYSIS FOLLOWING SURGERY: WHO SHOULD BE MONITORED?

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Introduction: To evaluate which patients might benefit from real-time ST segment analysis for detection of myocardial ischemia postoperatively, the prevalence of ST segment changes was correlated to preoperative cardiac risk factor assessment (tobacco use, hypertension, diabetes, angina, previous myocardial infarction, congestive heart failure)(1) in recovery room patients.

Methods: Preoperative risk factors and real-time ST segment monitoring were obtained from all patients ≥35yr (N=1183) after non-thoracic, non-intracranial surgery during a 5 month period. ST segments in ECG leads V5 and II were continuously analyzed and recorded (Marquette Electronics Series 7010 monitor, filter bandwidth 0.05-105Hz, gain 10mm=1mV, ST measurement 60 msec after J point) until recovery room discharge (mean time±SD=90±57min). For each lead, ST segment deviations from isoelectric lasting >2min were classified as either ST segment depression ≤-1mm (ST≤-1), ST segment elevation >1mm (ST>1), and/or ST segment elevation >2mm (ST>2). Nonparametric testing (Mann-Whitney test with Kolmogorov-Smironov two sample post-hoc test) was used to determine correlations between risk factors and ST changes. The effect of age <50yr on prevalence of ST changes was also analyzed. 209 patients (17.7%) were excluded due to incomplete risk factor or ST segment data (N=74), or direct intensive care admission (N=135).

Results: The study population (N=974) was predominantly male (N=954;95.9%) with mean age 61±12yr and a mean of 1.5±1.1 risk factors. **ST≤-1** occurred in 130 patients (13.6%); **ST>1** occurred in 133 patients (13.9%), with **ST>2** in 14 patients (1.5%). There was a positive correlation between increasing number of risk factors and **ST≤-1** and **ST>2** (p<0.01). Patients with >2 risk factors (N=149; 15.3%) had a 0.33 prevalence of **ST≤-1** and/or **ST>2**, but no patient with >2 risk factors and age <50yr had **ST≤-1** or **ST>2** (Figure 1b). Among patients with ≤2 risk factors (N=825; 84.7%), age <50yr significantly reduced the prevalence of **ST≤-1** and/or **ST>2** (p<0.01, Figure 1a).

Discussion: These results suggest that real-time ST segment monitoring be reserved for patients ≥50yrs, especially with >2 cardiac risk factors.

References: (1) Am J Cardiol 38:46,1976.

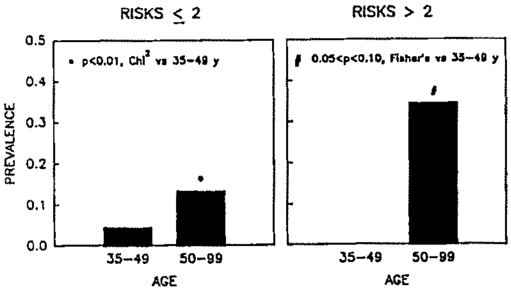

Figure 1. Prevalence of **ST≤-1** and/or **ST>2** by age group: (a) ≤2 risk factors, (b) >2 risk factors.

S44

TITLE: POSTOPERATIVE EPIDURAL OPIATE PHARMACOKINETICS

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AFFILIATION: Anes. Depts, University Hospitals, D-69 Heidelberg, FRG; Jerusalem*, Israel.

The aim of the study was to evaluate opiate concentrations (OC) under epidural patient controlled analgesia (ePCA) with hydrophilic morphine (MO) and lipophilic methadone (Meth), fentanyl (F) and sufentanil (S).

With institutional approval and informed written consent, 94 patients scheduled for abdominal operations received ePCA (loading doses (LD), basal infusions (BI), and on demand doses (OD) according to Table 1 when complaining of severe postoperative pain (>5, scale 0-10). Blood samples were taken at various intervals to determine serum Mo, F, and S by radioimmunoassay and plasma Meth by gas-chromatography (sensitivities (ng/ml): 0.1 (Mo), 0.01(F), 0.01(S), 0.5 ng/ml (Meth). For statistics ANOVA, repeated measurements ANOVA, and paired t-test were used.

Table 1

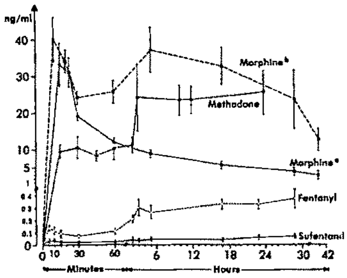
Dose	Mo_a+	Mo_b*+	Meth*+	F+	S+
LD (mg)	2	2	2	0.06	0.015
BI (mg/hr)	0.2	0.2	0.46	0.02	0.005
OD (mg)	0.6	0.6-2	0.2-1.0	12.5	3.1

+ = normal ward and * artificially ventilated intensive care patients

Pain was well controlled in all patients. Opiate concentrations (OC) are shown in Fig. 1.

Epidural hydrophilic and lipophilic OC differ significantly. Serum Mo peaked in the range causing systemic analgesia and decreased steadily thereafter (Mo^a p<0.001; Mo^b p<0.01). We postulate that the initial lipophilic OC plateaus are caused by local distribution at the site of injection and that protracted redistribution from slow distribution compartments results in opiate accumulation in the course of the treatment (p<0.001 Meth; p<0.05 F; NS S). The lower distribution volume of fentanyl compared with sufentanil may cause its more pronounced accumulation.

Figure 1



S45

TITLE: **POSTANESTHETIC HYPOXEMIA DUE TO REMOVAL OF SUPPLEMENTAL OXYGEN THERAPY**

AUTHORS: MS Cohen, M.D.; JH Eichhorn, M.D.; AH Darvish, B.A.
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Postanesthetic pts frequently remove their own supplemental O_2 therapy (O_2 Rx) or have it removed by hospital personnel (by custom or by protocol). Consequent otherwise undetected dramatic S_pO_2 decreases after PACU discharge were shown with telemetric continuous pulse oximetry. **METHODS:** With Committee on Clinical Investigations approval, 93 GA pts randomly selected by room gave informed consent to be monitored immediately upon arrival from PACU with a pulse oximeter (Nellcor N-200) connected to a Nellcor "Oxinet" computerized telemetric pulse oximetry network (TPON) which recorded S_pO_2 every 10 s. No data were displayed and O_2 Rx use was noted. TPON data were passed through a separate previously validated signal-processing algorithm[1] that rejects disconnects and artifacts before displaying and categorizing S_pO_2. Hypoxemia definitions-mild: 95-90%; moderate: 89-85%; severe: $\leq$ 84% ($<P_aO_2 = 54$ mmHg). **RESULTS:** Intermittent patient removal of O_2 Rx caused recurrent falls in S_pO_2 of >10% down to moderate and/or severe hypoxemia in 11 pts (e.g. Fig. 1). O_2 Rx removal the morning after surgery precipitated persistent hypoxemia in 15 pts: 9 mild, 4 moderate, and 2 severe (e.g. Fig. 2). **DISCUSSION:** Intermittent patient removal and premature discontinuation of O_2 Rx leads to potentially dangerous undetected hypoxemia in certain patients. When questioned, pts often failed to understand importance of O_2 Rx and staff often assumed no further need for O_2 Rx on day after surgery. Education is needed for both. Continuous TPON monitoring would identify pts at risk for hypoxemia and help better direct postanesthetic O_2 Rx.

[1] Pan PH, James CF. Anesthesiology 73:A543 and A943, 1990

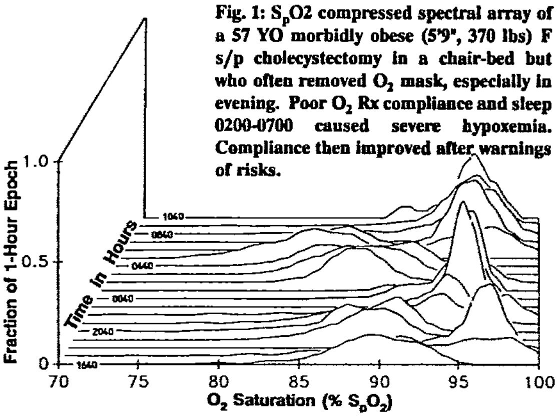
Fig. 1: S_pO2 compressed spectral array of a 57 YO morbidly obese (5'9", 370 lbs) F s/p cholecystectomy in a chair-bed but who often removed O_2 mask, especially in evening. Poor O_2 Rx compliance and sleep 0200-0700 caused severe hypoxemia. Compliance then improved after warnings of risks.

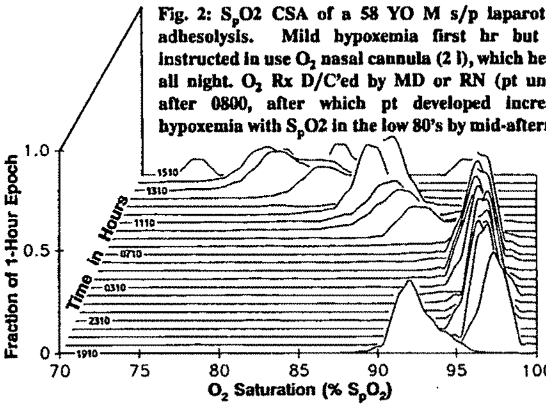
Fig. 2: S_pO2 CSA of a 58 YO M s/p laparotomy/ adhesolysis. Mild hypoxemia first hr but then instructed in use O_2 nasal cannula (2 l), which he wore all night. O_2 Rx D/C'ed by MD or RN (pt unsure) after 0800, after which pt developed increasing hypoxemia with S_pO2 in the low 80's by mid-afternoon.

S46

TITLE: **POST C/S EPIDURAL-PCA ANALGESIA: FENTANYL-BUPIVACAINE 0.01%-EPINEPHRINE VS. SUFENTANIL-BUPIVACAINE 0.01%-EPINEPHRINE**

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EJ Pantuck, MD, E Goodman, MD, J Brady, MD
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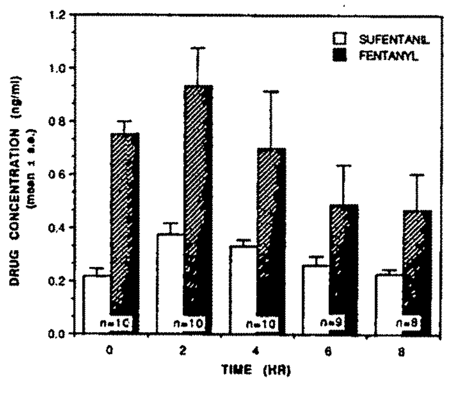
We compared quality of analgesia, dosage and side effects of epidural-PCA infusions of fentanyl-bupivacaine-epinephrine to sufentanil-bupivacaine-epinephrine. Following IRB approval, we conducted a double-blind study of 250 consenting pts scheduled for elective C/S and not receiving systemic opioids. Upon arrival in the PACU pts were randomized to 2 epidural-PCA infusion groups: Group I (n = 125) fentanyl 2μg/mL with bupivacaine 0.01% and epinephrine 0.5μg/mL; Group II (n = 125) sufentanil 0.8μg/mL with bupivacaine 0.01% and epinephrine 0.5μg/mL. The initial infusion rate was 16mL/hr. Pain and overall satisfaction were assessed with a 10-point scale. At intervals following discontinuation of the infusion, plasma samples were obtained for determination of opioid concentrations. RESULTS: The overall satisfaction scores were 8.7±0.1 for Group I and 9.1±0.1 for Group II (p=.06). Pain relief was satisfactory in both groups and all pts could easily ambulate. Infusion durations for Groups I and II were 50.4±1.6 and 53.5±1.6 hrs, respectively. The number of times PCA requests were made was higher ($p < .05$) for Group I than for Group II (106.7±28 vs 70.8±12). There were no differences between the groups with respect to incidence of side effects (Table). No pt had urinary retention or a respiratory rate < 12 br/min. Two hrs after discontinuation of the infusion, plasma sufentanil and fentanyl levels were a mean of 86%, and 32% higher, respectively ($p < .01$) than at the time of discontinuation (Figure). CONCLUSION: Epidural-PCA in both groups was without serious side effects and achieved a high level of satisfaction.

SIDE EFFECTS	GROUP I		GROUP II	
	n	%	n	%
Pruritus (Total)	87	69.6	84	67.2
Treated	17	13.6	15	12
Sedation (Total)	65	52	76	60.8
Treated	0	0	0	0
Nausea	11	8.8	15	12
Vomiting	6	4.8	15	12
Urinary Ret	0	0	0	0
Resp Rate < 12	0	0	0	0



S47

TITLE: EPIDURAL ANALGESIA FOR LABOR: FENTANYL-BUPIVACAINE-EPINEPHRINE VS. SUFENTANIL-BUPIVACAINE WITH AND WITHOUT EPINEPHRINE

AUTHS: S Cohen, MD, D Amar, MD, CB Pantuck, BA, EJ Pantuck, MD, R Kanas, MD, N Singer, MD
AFFIL: Depts Anesth Albert Einstein Coll Med, Bronx, NY 10461; Columbia U Coll of Phys & Surg, NY 10032

We compared epidural infusions of fentanyl bupivacaine-epinephrine to sufentanil-bupivacaine with and without epinephrine with regard to analgesia and side effects. Following IRB approval, we conducted a double blind study of 150 consenting pts during labor and delivery. Pts received no systemic opioids and were randomized to 3 groups as shown in Table I. After a test dose of 3mL 3% 2-chloroprocaine pts received a 20mL loading dose of the study solution. An infusion was then started at 10mL/hr. Pain and overall satisfaction were assessed with a 10-point scale. For inadequate analgesia, two 5mL boluses of the study solution were given 15 min apart. If analgesia was still inadequate, additional 5 ml boluses of 0.25% bupivacaine were given as needed. Plasma samples for opioid determinations were obtained from the mother and from the umbilical cord vein at the time of delivery.

Results: There were no differences among the 3 groups with respect to infusion duration, total volume of study solution administered, side effects (Table 2), duration of 1st or 2nd stage of labor or outcome of labor, or neonatal Apgar scores. Overall satisfaction for Group I (8.6) was lower ($p<0.01$) than for Groups II (9.3) or III (9.6). Plasma opioid levels are shown in the figure below. More pts in Group I (42%) requested additional 0.25% bupivacaine than in Group II (6%) or Group III (4%) ($p<0.0001$).

Conclusions: Epidural opioid infusion was without serious side effects in all groups. Pts receiving sufentanil were more satisfied and requested considerably less 0.25% bupivacaine.

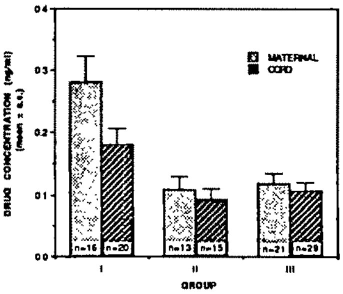
TABLE 1: EPIDURAL INFUSION CHARACTERISTICS

GROUP	FENTANYL	SUFENTANIL	BUPIVACAINE	EPINEPHRINE
I: n=50	2µg/mL	—	0.015%	2µg/mL
II: n=50	—	1µg/mL	0.015%	2µg/mL
III: n=50	—	1µg/mL	0.03%	—

TABLE 2. SIDE EFFECTS

	I		II		III	
	n	%	n	%	n	%
Pruritus	31	62	39	78	31	62
Treated	1	2	1	2	4	8
Sedation	27	54	31	62	25	50
Treated	0	0	0	0	0	0
Nausea	4	8	3	6	2	4
Vomiting	3	6	3	6	2	4
Urinary Ret	12	24	8	16	18	36
Resp <12	0	0	0	0	0	0

FIGURE



S48

TITLE: INDWELLING SPINAL CATHETERS AND POST DURAL PUNCTURE HEADACHES

AUTHS: S Cohen, M.D., N Singer, M.D., D Amar, M.D., M Umanoff, M.D., E Goodman, M.D.
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It has been suggested that continuous spinal anesthesia is associated with a low incidence of post-dural puncture headache (PDPH) in non-obstetric pts (1). Placement of spinal catheters for a short duration (<24hrs) in obstetric pts did not reduce the incidence of PDPH (2). This study was designed to determine whether continuous spinal catheterization >24 hrs is associated with less PDPH.

METHODS: Following IRB approval charts of 63 parturients who had an accidental dural puncture following epidural block from January 1987 through July 1990 at our institution were reviewed. Epidural block was attempted using 17 gauge Touhy needles and 19 gauge epidural catheters. Three groups were identified (Table 1) Group I (n=24) pts had a dural puncture on the first attempt of epidural block, but a successful epidural block on a repeat attempt. Group II (n=26) pts had a dural puncture with immediate conversion to continuous spinal block and the epidural catheter left in situ <24hrs. Group III (n=13) pts had an immediate conversion to spinal block and the epidural catheter left in situ >24 hr. Parturients were followed until discharge (2-5 days) and by phone for a week. PDPH was treated as per conventional practice.

RESULTS: There were no demographic differences among the groups. No pt in Group III developed PDPH (Table 2). The incidence of PDPH for Group I or II was higher than for Group III. There was no difference between Group I and II with regard to requests for a blood patch.

CONCLUSION: Our results strongly suggest that indwelling spinal catheterization > 24hrs following accidental dural puncture in parturients may be an adequate method of PDPH prophylaxis.

Refs: 1. Anesth Analg 66:791-794,1987
2. Anesthesiology 71:A723, 1989

TABLE 1. DURATION OF INTRATHECAL CATHETERIZATION

		Duration (hrs)		
	(n)	Mean	SD	Range
Group I	24	0	0	0
Group II	26	8.3*	4.7	2-22
Group III	13	37	9.7	24-54

* p < .001 Group II vs III

TABLE 2. PDPH: INCIDENCE AND TREATMENT

	PDPH		Blood Patch	
	(n)	(%)	(n)	(%)
Group I	10	41.7	7	70
Group II	12	46.1	6	50
Group III	0*	0	0	0

* p < .01 Group III vs. Group I or II

S49

Title: HYPERTENSION AFTER CEREBRAL ISCHEMIA IN RATS: THE EFFECT ON BRAIN INJURY AND EDEMA

Authors: DJ Cole MD, RM Schell MD,
JC Drummond MD, P Patel MD
Affiliation: Anesthesiology Departments, Loma Linda University, Loma Linda, CA; and UC San Diego, La Jolla, CA.

Introduction: During complex neurosurgical procedures, prolonged periods of temporary vascular occlusion may be required. After episodes of transient cerebral ischemia, the brain is susceptible to additional injury via hypoperfusion deficits.[1] Although increases in mean arterial pressure (MAP) improve perfusion, such therapy conveys a risk of vasogenic edema.[2] We assessed the effect of phenylephrine-induced hypertension on brain injury and edema in rats, after temporary middle cerebral artery occlusion (MCAo).

Methods: Following approval by the Animal Care Committee, rats were anesthetized with 1.2 MAC isoflurane and MCAo maintained for 180-min. During a 120-min period of reperfusion each rat received one of the following blood pressure regimens: **Control** (n = 16)-normotensive reperfusion; **90/HTN** (n = 16)-MAP was increased by 30 mmHg for the first 90-min of reperfusion, followed by 30-min of normotension; **15/HTN** (n = 16)-30 min of normotension, followed by 15-min of hypertension and 45-min of normotension.

Part A: 30 $mg \cdot kg^{-1}$ of Evans Blue (EB) was given (↑EB in brain≈↑edema) to 8 rats in each group. The brains were harvested and analyzed for EB by spectrophotometry.

Part B: for the 8 remaining rats in each group, the brains were analyzed for injury with TTC stain, and for edema by microgravimetry.[3] The data were compared by an analysis of variance and t-tests.

Results: Evans Blue was greater in the 90/HTN group vs the other two groups. Cerebral injury and brain water (specific gravity) were less in the 15/HTN group vs the 90/HTN group, which was in turn less than the Control group (see Table 1).

Discussion: This study supports a hypothesis that after transient cerebral ischemia, a short period of hypertension decreases brain injury. A longer duration of hypertension appears to increase the risk of vasogenic edema.

Group	EB	Injury	Sp. Grav.
Control	11±4	41±7	1.036±0.002
90/HTN	22±7*	30±7†	1.040±0.002†
15/HTN	9±4	18±6‡	1.043±0.001‡

Table 1-EB ($\mu g \cdot g^{-1}$ of brain), brain injury (% of ischemic hemisphere), and specific gravity (mean±SD). *$p<0.05$ vs the Control and 15/HTN groups. †$p<0.05$ vs the Control. ‡$p<0.05$ vs the Control and 90/HTN groups.

References:
1. *J Neurosurg* 63:272-277, 1985.
2. *J Neurosurg* 59:803-809, 1983.
3. *Am J Physiol* 259:H211-H217, 1990.

S50

Title: HEMODILUTION DURING CEREBRAL ISCHEMIA IN RATS: EFFECTS OF STROMA-FREE HEMOGLOBIN ON BRAIN INJURY

Authors: DJ Cole MD, RM Schell MD,
JC Drummond MD, RJ Pryzbelski MD
Affiliation: Anesthesiology Departments, Loma Linda University, Loma Linda, CA; and UC San Diego, La Jolla, CA.

Introduction: During high risk surgical procedures for cerebral ischemia, hemodilution has been proposed to ameliorate brain injury. However, the efficacy of hemodilution therapy is limited by an accompanying decrease in oxygen content.[1] We assessed the effect of hemodilution, with stroma-free hemoglobin (SHgb, 7 $g \cdot dl^{-1}$), on brain injury and edema after middle cerebral artery occlusion (MCAo) in rats.

Methods: After approval by the Animal Care Committee, rats were anesthetized with 1.2 MAC isoflurane. One of the following protocols were maintained during 180-min of MCAo and 120-min of reperfusion. Donor blood was given to maintain an equal volume state between groups.

Control (n = 7)-hematocrit (Hct) ≈44%.
30/Hct/Norm (n = 7)-Hct ≈16%.
30/Hct/HTN (n = 7)-Hct ≈16%.

In the 30/Hct/Norm group, SHgb was infused over a 90-min period before MCAo. By this means mean arterial pressure (MAP) was stable. In the 30/Hct/HTN, SHgb was given as a bolus 15-min prior to MCAo. By this means a 25-30 mmHg increase in MAP was produced during MCAo. After the 5-hr period of MCAo and reperfusion, the brains were harvested and analyzed for injury with TTC stain, and for edema by microgravimetry.[2] All data were compared by analysis of variance and t-tests.

Results: Brain injury was less in the 30/Hct/HTN group vs the 30/Hct/Norm group; which was in turn less than the Control group ($p<0.05$, see Table 1). Specific gravity was greater in both 30/Hct groups vs the Control group ($p<0.05$).

Discussion: The results of this study are consistent with a hypothesis that hemodilution with SHgb decreases brain injury and edema after temporary focal cerebral ischemia. In addition, if SHgb is delivered in a manner during which an inherent hypertensive response is manifested further brain protection is conveyed.

Group	Injury	Sp. Grav.
Control	46±5	1.037±0.003
30/Hct/Norm	34±7*	1.043±0.002*
30/Hct/HTN	25±2†	1.044±0.002*

Table 1-Brain injury (% of ischemic hemisphere), and specific gravity (mean±SD). *$p<0.05$ vs the Control group. †$p<0.05$ vs the Control and 30/Hct/Hct groups.

References:
1. *Stroke* 20:423-427, 1989.
2. *Am J Physiol* 259:H211-H217, 1990.

S51

Title: HEMODILUTION WITH STROMA-FREE HEMOGLOBIN DOES NOT AFFECT ISOFLURANE MAC IN RATS

Authors: D.J. Cole M.D., R.M. Schell M.D.,
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Affiliation: Anesthesiology Department, Loma Linda University, Loma Linda, CA.

Introduction: Stroma-free hemoglobin (SHgb) has been developed as a resuscitative and therapeutic fluid for many clinical situations. Although isovolemic anemia has not been shown to affect MAC;[1] in a variety of animal models, during the hypervolemic administration of SHgb an immediate increase in blood pressure (30-40 mmHg) is consistently observed. We postulated that this increase in blood pressure might reflect a change in anesthetic state. Accordingly, the affect of hemodilution, with stroma-free hemoglobin (SHgb, 7 $g \cdot dl^{-1}$), on isoflurane MAC was assessed in rats.

Methods: Following approval by the Animal Care Committee, age matched Spontaneously Hypertensive Rats were anesthetized with 1.2 MAC isoflurane for a 90-min equilibration period.[2] Each animal was given SHgb to achieve one of the following hematocrits (Hct):

Isovolemic Control (n=6)-Hct 44%.
44/Hct, Hypervolemic (n=6)-Hct 44%.
30/Hct, Hypervolemic (n=6)-Hct 30%.
16/Hct, Hypervolemic (n=6)-Hct 16%.

Donor blood was given to maintain an equal blood volume between all hypervolemic groups. MAC was determined using the standard tail clamp technique.[3] The data were compared by analysis of variance with t-tests and a Bonferroni correction factor.

Results: The isoflurane requirement to achieve 1.0 MAC was not different between any of the four groups (see Table 1).

Discussion: The results of this study are consistent with previous investigators[1] who have shown that anemia does not affect MAC (provided arterial oxygen content does not decrease below 4.3 $ml \cdot dl^{-1}$). The hemodynamic response to SHgb is not yet explained.

Group	Isoflurane MAC
Isovolemic Control	1.48±0.07
44/Hct	1.44±0.08
30/Hct	1.49±0.10
16/Hct	1.47±0.12

Table 1-Isoflurane MAC (mean±SD).

References:
1. *Anesthesiology* 32:35-45, 1970.
2. *Lab Anim Sci* 40:506-509, 1990.
3. *Anesthesiology* 53:315-334, 1980.

S52

Title: CARDIOVASCULAR STABILITY WITH RAPID INTRAVENOUS INFUSION OF ONDANSETRON

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Introduction: Ondansetron (Glaxo), a serotonin (5-HT) antagonist, has found clinical use as an antiemetic agent in patients undergoing chemotherapy. An injectable form of the drug is being evaluated for prevention and therapy of postanesthetic nausea and vomiting. This study investigated the cardiovascular effects of rapid intravenous administration of ondansetron.

Methods: Institutional Review Board approval was obtained for the study. Seventy-one women scheduled for outpatient surgery requiring general endotracheal anesthesia granted informed consent. They were randomly assigned to receive 20 ml of a saline solution which contained 0, 1, 4, or 8 mg of ondansetron. After preanesthetic evaluation, an intravenous infusion of D5/0.45 NaCl was begun, the patient taken to the operating room and supine baseline measurements of heart rate, blood pressure, respiratory rate and oxygen saturation recorded. No preanesthetic medication was administered. The study drug was then infused intravenously over two minutes. The variables noted above were recorded at the beginning and the end of the infusion and once per minute for five minutes after the end of the infusion. Significant differences were sought using ANOVA. $p<0.05$ was considered significant.

Results: The groups were comparable in age, weight, and pre-study vital signs. Mean change in the variables between the start of the infusion and 5 minutes after cessation of the infusion are shown in the table.

			CHANGE IN:				
Group	N	Dose	HR	SBP	DBP	RR	SAO2
		mg	/min	mmHg	mmHg	/min	%
1	18	0	-0.3	-7.8	-8.5	+0.4	+0.3
2	18	1	-3.8	-5.6	-3.9	-0.3	-1.9
3	16	4	+3.1	-1.0	+1.5	-0.2	-0.2
4	19	8	+5.8	-8.9	-6.8	0	+0.2

Typical clinical variation occurred, but none of the groups showed a statistically significant difference from control for any variable at any point in the study.

Discussion: The role of 5-HT in cardiovascular homeostasis is unclear. The compound is a significant constrictor in some vascular beds (5-HT_2 mediated), and is thought to be a vasodilator in some beds when acting on the 5-HT_3 receptor. Administration of a 5-HT_3 antagonist might be expected to lead to an increase in blood pressure and a reflex decrease in heart rate. However, 5-HT_3 antagonists have been shown to act directly at the afferent nerves in cardiac muscle to block 5-HT induced bradycardia. We were unable to demonstrate any consistent cardiovascular effect from rapid I.V. administration of ondansetron. The changes we did find may actually represent decreases in anxiety levels as the patients became more comfortable with their surroundings. A drug which holds promise as a prophylactic antiemetic for surgical patients appears to have no clinically important cardiovascular effects when administered in this fashion to conscious unsedated patients.

S53

TITLE: THE EFFECT OF KETAMINE ON 3,4-DIHYDROXYPHENYLGLYCOL (DOPEG) OVERFLOW IN ISOLATED FERRET MYOCARDIUM

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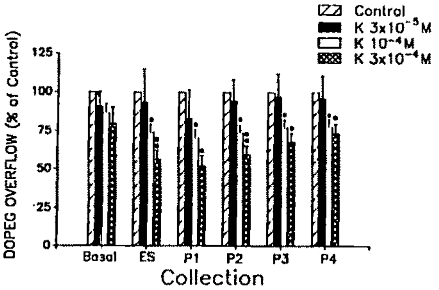
It has been shown previously that ketamine increases the overflow of norepinephrine (NE) from isolated superfused ferret ventricular myocardium (1). The purpose of this study was to determine if ketamine inhibits the neuronal reuptake of NE as evidenced by decreases in the overflow of the neuronally derived NE metabolite DOPEG.

METHODS: In superfused (2 ml/min), ferret right ventricular myocardial strips, we measured ketamine's effect on DOPEG efflux under basal conditions, during electrical field stimulation (ES) (10 V, 2 Hz) and in four post stimulation collection periods (P1, P2, P3, P4). All collections were 10 minutes. All tissues were exposed to corticosterone (4×10^{-5}M) and yohimbine (10^{-7}M); one muscle strip served as control and others were exposed to a single concentration of ketamine (3×10^{-5}, 10^{-4} or 3×10^{-4}M). DOPEG in superfusate was quantified by high pressure liquid chromatography with electrochemical detection (2).

RESULTS: Ketamine 10^{-4} and 3×10^{-4}M produced significant decreases in DOPEG overflow during ES and in all post-stimulation recovery periods (Figure). DOPEG overflow was decreased by approximately 25% relative to control at both concentrations in each collection period.



Effect of ketamine on DOPEG overflow in isolated myocardial strips. Data are mean ± SE (n=7). *P < 0.05, **P < 0.01 vs control by repeated measures ANOVA followed by Dunnett's test.

DISCUSSION: DOPEG overflow serves as an index of the reuptake of NE by adrenergic nerve terminals (3). We hypothesized that if ketamine impaired this reuptake mechanism, DOPEG overflow should decrease. A decrease was detected at 10^{-4} and 3×10^{-4}M. These data support the hypothesis that ketamine's positive inotropic effect in isolated myocardium results from the inhibition of the neuronal reuptake of NE (4).

References
1. Cook DJ, et al: FASEB J 5:A1220, 1991.
2. Hunter LW, et al: Anal Biochem 173:340-352, 1988.
3. Rorie DK, et al: Am J Physiol 257:H1945-H1951, 1989.
4. Cook DJ, et al: Anesthesiology 74:880-888, 1991.

S54

TITLE: DOES EPIDURAL BUTORPHANOL PROVIDE SAFE AND EFFECTIVE ANALGESIA FOR CHRONIC LOW BACK PAIN?

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Degenerative joint and lumbar disc disease can result in chronic low back pain limiting normal behavior. Epidural steroids, local anesthetics and opioids have been used to treat chronic back pain but each has limitations in dosage frequency, duration of effect and safety. The use of epidural opioids, acting on the mu receptor is limited by the high incidence of urinary retention, histamine release evidenced by pruritus and bronchoconstriction, and late respiratory depression. Therefore epidural narcotics are rarely used to treat outpatient chronic pain patients.

Butorphanol is a kappa receptor agonist with possible activity at the sigma receptor and is a mu antagonist. Since the kappa, not the mu, receptor is the site of spinal analgesia, theoretically epidural butorphanol could provide pain relief for patients with low back pain. This is the first reported series of an epidural kappa agonist to treat chronic low back pain.

Method: Six male patients (ages 30-76) with chronic degenerative joint and/or disc disease received a series of epidural butorphanol injections over two years (n=49). The efficacy, duration and side effects were compared with epidural local anesthetics and steroids.

Results: 67% of the epidural butorphanol blocks resulted in significant pain relief for an average of 12.5 days (decreasing oral analgesic use of 50-100% and increasing activity). In comparson, in the same patients, a prior series of local anesthetic and steroid injections resulted in a 50% success rate with relief lasting slightly less than 10 days. Post epidural butorphanol complications were sedation (88%), nausea (26%) and dizziness (2%). Complications associated with the sigma receptor agonists such as dysphoria, hallucinations or delusions were not observed.

Discussion: In the treatment of chronic low back pain epidural local anesthetics have a limited duration of action and epidural steroids have a maximum recommended dosage. Epidural opioids have not been used to treat chronic pain in outpatients because of the high incidence of urinary retention, pruritus and nausea and the possibility of delayed respiratory depression. The use of butorphanol, by acting primarily at the kappa receptor and as a partial antagonist at the mu receptor, is not limited by these side effects. In addition, unlike pure mu agonists, there is a low physical dependence liability and limited development of tolerance with the use of this drug. The most commonly reported side effect of butorphanol in this and other studies is sedation. This effect was considered a beneficial byproduct of analgesia by our patients.

S55

TITLE: PERSONALITY PARAMETERS AND CLINICAL EXPECTATIONS OF ANESTHESIA AND SURGICAL RESIDENTS AND STAFF

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Personality and expectations may play a significant role in professional interactions. The goal of this study was to determine differences between staff and resident surgeons and anesthesiologists.

Methods: The Eysenck Personality Inventory (EPI) measures personality in terms of two pervasive independent dimensions: neuroticism-stability and extraversion-introversion. The EPI was administered along with a set of skills (listed below) to be ranked in order of importance for the practice of anesthesiology and surgery:

Patient rapport and compassion
Effective communication in O.R.
Preoperative medical evaluation
Competence in emergency situation
Technical skill and speed
Service and availability

The EPI was scored and results were compared with specific groups of the population.

Results: On the neuroticism-stability dimension all groups were stable. However, staff physicians scored higher on the stability dimension than the residents. Surgery residents were the most extroverted group, scoring similarly to salesmen and surgery staff the most introverted, scoring similarly to managerial workers. Anesthesia residents and staff were intermediate in this scale, scoring similarly to secretaries.

The rank order of importance of specific clinical parameters for the practice of anesthesiology and surgery by each group are seen in Table 1.

I. ANESTHESIOLOGY	Most Important	Least Important
Anesth Staff	Emergency	Service
Anesth Res.	Emergency	Service
Surgery Staff	Emergency	Compassion
Surgery Res.	Emergency	Compassion
II. SURGERY	Most Important	Least Important
Anesth Staff	Compassion	Service
Anesth Res.	Skill/speed	Service
Surgery Staff	Compassion	OR Communication
Surgery Res.	Skill/speed	Service

Discussion: Note that surgeons rank compassion highly for themselves but do not consider it important for anesthesiologists. Also, unlike staff physicians, residents seem to consider skill and speed more important for surgeons than compassion. Understanding the differing perspectives between surgical and anesthesia staff and residents may have implications for clinical training and intraoperative interactions.

S56

TITLE: THE HYPNOTIC RESPONSE TO THE α_2 ADRENERGIC AGONIST, DEXMEDETOMIDINE, IS BLOCKED BY ROLIPRAM AND DIBUTYRYL CYCLIC AMP IN THE RAT

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INTRODUCTION:The α_2 adrenergic agonists (α_2 aa) are a novel class of hypnotic-anesthetic agents with selectivity for specific binding sites through which these compounds exert their pharmacologic response[1]. This selectivity facilitates a systematic characterization of the molecular mechanism of anesthetic action including the sites of activity of α_2 aa in the brain. Previously we showed that the locus ceruleus (LC) is a pivotal site for the hypnotic response to dexmedetomidine (DEX), a highly-selective α_2 aa[2]. This precise localization now allows us to discretely probe the post-receptor molecular mechanism for the hypnotic action of α_2 aa. In this study we address the role of adenylate cyclase by methods designed to sustain cAMP levels.

METHODS: Cannulae were inserted stereotaxically into the LC of halothane-anesthetized rats (n=45). Following an elapsed period of at least 48 h, rats were tested for duration of loss of righting reflex ("sleep-time") in response to administration of DEX 7 µg LC. Rolipram, a selective brain phosphodiesterase inhibitor which prevents the breakdown of endogenous cAMP, was administered 0.3 mg/kg ip, 1 min prior to DEX LC. In another set of experiments, dibutyryl cAMP (db cAMP), a permeable, non-hydrolysable cAMP analog, was administered into the LC (4 to 400 pg) 1 min prior to LC DEX. Following the conclusion of each experiment, the correct placement of the cannula was identified histologically.

RESULTS: Data are presented from 30 rats in which correct placement of the cannula was verified. The sleep-time following DEX LC was 55min (±10).Both rolipram (n=4) and db cAMP (n=3) when given alone produced stereotypic behavior in the rats. Rolipram completely blocked the hypnotic response to LC DEX. Dibutytryl cAMP dose-dependently blocked the hypnotic response such that no animal lost its righting response at 400 pg LC.

DISCUSSION & CONCLUSIONS:The α_2 adrenoceptors are negatively coupled to adenylate cyclase in many biologic systems. After activation of α_2 adrenoceptors by agonists such as DEX, intracellular cAMP decreases, which limits the activation of cAMP-dependent protein kinase. This enzyme phosphorylates and thereby modulates the activity of regulatory proteins which could include ion channels to change the membrane potential of the excitable neuron. If a decreased level of cAMP is important in the transduction of the hypnotic reponse to DEX through the above-mentioned cascade, then strategies designed to artificially maintain cAMP should counteract this hypnotic response. Our findings suggest that inhibition of adenylate cyclase is necessary for the transmembrane signalling of the hypnotic response to DEX.

REFERENCE: 1.Anesthesiology 71:75-79, 1989.
2.Anesthesiology 75: In Press, 1991.

ACKNOWLEDGEMENTS:NIH(GM30232),VA,&,Farmos Res Group.

S57

TITLE: RIBOSYLATION OF G PROTEINS IN THE LOCUS CERULEUS OF RATS PREVENTS THE HYPNOTIC/ANESTHETIC ACTION OF THE α_2 ADRENERGIC AGONIST, DEXMEDETOMIDINE

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INTRODUCTION: The α_2 adrenergic agonists ($\alpha_2$aa) produce an hypnotic-anesthetic action in rats when administered directly into the locus ceruleus (LC)[1]. The mediating mechanism for this anesthetic action involves a guanine-nucleotide binding protein (G Protein) which couples the receptor to the effector mechanism. The G proteins which couple to inhibitory neurotransmitter receptors are susceptible to inactivation by ADP-ribosylation in the presence of pertussis toxin (PTX). We therefore sought to determine whether PTX administered into the LC prevents the hypnotic response to dexmedetomidine (DEX), a highly-selective $\alpha_2$aa.

METHODS:Cannulae were inserted stereotaxically into the LC of halothane-anesthetized rats (n=55). Following an elapsed period of at least 48 h, rats were administered either PTX, 0.3 µg LC or an equal volume (0.5 µl) of the buffer. After an additional 5 days, each cohort was further subdivided into groups which received either DEX 7 µg LC or an equal volume (0.2 µl) of saline LC and were tested for duration of loss of righting reflex (LORR). The following day all the rats were sacrificed, the LCs from both the cannulated and non-cannulated sides were harvested and plasma membranes prepared. Membranes were exposed to PTX *in vitro* in the presence of ^{32}P-labelled NAD to ribosylate remaining functional G Protein. The proteins were separated on PAGE and prepared for autoradiography and assessment by laser densitometry.

RESULTS: In the vehicle-treated cohort which subsequently received DEX, 15 of 16 rats lost their righting reflex for a mean (±SD) duration of 56 min(± 9). Only 1 of 16 PTX-treated rats exhibited a LORR for 30 min. In the "back-titration" method for evaluation of ribosylation, the G proteins from the vehicle-treated rats incorporated more ^{32}P-labelled NAD. This indicates that these proteins were more susceptible to *in vitro* ribosylation because they were not denatured by prior treatment. Conversely, rats treated with PTX had their G proteins rendered dysfunctional by *in vivo* ribosylation which were not readily identified by NAD-labelling *in vitro*.

DISCUSSION & CONCLUSIONS: These data demonstrate conclusively that the hypnotic response to $\alpha_2$aa requires the participation of PTX-sensitive G proteins in the transmembrane signalling pathway in the rat locus ceruleus. There are many species of PTX-senstivie G proteins and we are currently characterizing the relevant subtype by immunoblotting techniques. Whether these G proteins transduce other anesthetic action is not known.

REFERENCE: Anesthesiology 75: In Press, 1991.

ACKNOWLEDGEMENTS: NIH(GM30232),VA,&,Farmos Res Group.

S58

Title: MODIFICATION OF BAROREFLEX EVOKED CORONARY VASODILATATION BY ENFLURANE ANAESTHESIA IN THE DOG

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Enflurane anaesthesia disturbs baroreflex-heart rate function[1], but little is known about effects on baroreceptor control of the coronary circulation. Confounding actions of ventricular rate (VR) on myocardial blood flow and basal anaesthesia complicate such analyses. The aim of this study was to examine the baroreceptor mediated coronary vasodilator reflex under conditions of controlled VR in a chronic canine preparation before and during enflurane anaesthesia.

Mixed breed dogs were examined three weeks after experimental complete heart block with ventricular pacing, and placement of pulsed Doppler flow probes on the circumflex, right and anterior descending coronary arteries. Measurements of coronary flow and arterial pressure were made while conscious, and during enflurane anaesthesia (1 MAC), at VRs 60, 100 and 180 min^{-1}, under resting conditions, and during stimulation of baroreceptors by elevations of arterial pressure with an intra-aortic balloon.

Balloon inflation led to an increase in aortic pressure to 127% of resting control both before and during anaesthesia. In the circumflex bed (n=9), there were no coronary conductance changes at VR 60 min^{-1} after balloon inflation, either awake, or following enflurane. At VRs 100 and 180 min^{-1} there were increases in conductance to 123% and 111% of control ($p<0.001$ and 0.05) which were abolished by enflurane anaesthesia. Similar responses in the right coronary bed in conscious dogs (n=9; 113% of control at VR 100 and 180 min^{-1}, $p<0.05$) were also abolished by enflurane. However baroreceptor stimulation had no significant effects on the anterior descending bed conductance (n=5) either before or during anaesthesia.

This study supports previous work with halothane[2] and isoflurane[3] suggesting that regional myocardial oxygen supply could be at risk during acute elevations in aortic pressure under volatile anaesthesia.

1. Acta Anaesthesiol Scand (1985) 29:90-94
2. Proc IUPS (1989) XVII:P5380
3. Proc APPS (1990) 21(2):187P

S59

Title: ISOFLURANE DEPRESSES LOAD INDEPENDENT BUT NOT LOAD DEPENDENT INDICES OF CARDIAC SYSTOLIC FUNCTION IN CHILDREN.

Authors: MW Crawford, MBBS, FRCPC; C Boutin, MD, FRCPC; J Dyck, MD, FRCPC
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Introduction. Several indices of systolic function, including ejection fraction, peak aortic flow velocity and ejection force, are dependent on left ventricular (LV) loading conditions. Using transesophageal echocardiography (TEE) in children, the effect of isoflurane on these load dependent indices was compared with its effect on a load independent measure of systolic function, the end-systolic wall stress/velocity of circumferential fiber shortening relation.[1]

Methods. Institutional approval and informed consent were obtained to study 5 ASA 1 or 2 children, aged 2 to 7 years, undergoing elective urologic surgery. After induction with isoflurane, vecuronium 0.15 $mg.kg^{-1}$ iv was administered and the trachea intubated. Ventilation was controlled to maintain normocarbia and a continuous caudal block was established. Ringers lactate, 10 $ml.kg^{-1}$ iv, was administered and 0.5, 1.0, or 2.0 MAC (age-corrected) isoflurane, in O_2/air, was delivered in random sequence. Vecuronium was administered as required. End-tidal isoflurane concentration was monitored using a Datex Capnomac 2. After 45 min at each concentration, simultaneous recordings of the LV 2-D and M-mode transesophageal echocardiogram, external carotid pulse tracing, and ECG were obtained by a blinded investigator using an Aloka SSD-870 Doppler ultrasound system with 5 MHz biplane phased array and pulse wave transducers. Systolic, mean and diastolic bp were measured with a Lifestat 200 BP monitor. To calculate LV ejection fraction, LV dimension was measured at end-systole and end-diastole by M-mode. Stroke volume index (SVI) was calculated as the product of aortic cross sectional area and velocity time integral divided by body surface area. The aortic root was visualized in the longitudinal plane and aortic value area was calculated as previously described.[2] Cardiac index (CI) was calculated as the product of SVI and heart rate (HR). To determine LV ejection force,[2] peak aortic flow velocity (PkV), time to PkV, and velocity time integral of acceleration were measured from aortic flow velocity spectra. To calculate LV wall stress at end-systole (WSes),[1] end-systolic pressure was determined by linear interpolation to the dicrotic notch of the carotid tracing and LV end-systolic internal dimension and posterior wall thickness were measured by M-mode. To calculate the velocity of circumferential fiber shortening[1] (Vcf), LV percent fractional shortening was determined[1] and LV ejection time was measured from the aortic flow velocity spectra. Vcf was rate-corrected (Vcfc) by dividing by √RR interval. Measurements were made in 3 cardiac cycles and mean values were calculated. Statistical significance ($p<0.05$) was determined using one-way analysis of variance, and intergroup differences by the least significant difference method.

Results. Values for HR and the load dependent indices of LV systolic function did not differ among the groups. Mean arterial pressure (MAP) and WSes, a measure of afterload, decreased in a dose-dependent fashion. WSes/Vcfc at 1.0 and 2.0 MAC were lower than that at 0.5 MAC (Table).

Hemodynamic Variable	0.5 MAC	1.0 MAC	2.0 MAC
HR (min^{-1})	115 ± 17	116 ± 26	119 ± 11
MAP (mmHg)	89 ± 7	61 ± 3*	52 ± 3†
Ejection fraction (%)	65 ± 7	63 ±10	61 ± 8
% Fractional shortening	35 ± 5	33 ± 8	32 ± 5
SVI ($ml.m^{-2}$)	35 ± 9	27 ± 6	38 ± 4
CI ($L.min^{-1}.m^{-2}$)	4.4 ± 1.6	3.5 ± 1.1	4.2 ± 1.0
PkV ($cm.s^{-1}$)	104 ± 16	104 ± 21	106 ± 17
Ejec force index ($kg.m.s^{-2}m^{-2}$)	0.17±0.03	0.19±0.07	0.17±0.07
WSes ($g.cm^{-2}$)	89 ±13	57 ± 7*	34 ± 10†
Vcfc ($circ.s^{-1}$)	0.93±0.07	0.95±0.25	0.92±0.05
WSes/Vcfc ($g.cm^{-2}.circ^{-1}.s$)	96 ± 14	60 ± 8*	37 ± 11†

* $p<0.05$ vs 0.5 MAC. † $p<0.05$ vs 1.0 MAC.

Discussion. The reduction in the WSes/Vcfc relation is consistent with a reduction in cardiac systolic function. The apparent stability of systolic function with load dependent indices may be attributed to the reduction in afterload (WSes). Determination of the WSes/Vcfc relation using TEE provides a relatively non-invasive in-vivo means to study cardiac systolic function during anesthesia.

Ref: 1. J Am Coll Cardiol 4: 715-24, 1984. 2. Am J Cardiol 64: 81-7, 1989

S60

Title: TIME-DEPENDENT RECOVERY OF CORONARY VASCULAR TONE DURING EXPOSURE TO ISOFLURANE IN DOGS

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Introduction. Previous studies have suggested time-dependent adaptation of systemic and cerebral circulations to vasodilating effects of isoflurane (1), but it is unknown whether this phenomenon extends to the coronary circulation. Accordingly, the present study was performed to evaluate changes in coronary blood flow (CBF) during continuous 3-hr exposure to isoflurane. To avoid complication of changes in systemic hemodynamics and global cardiac work, an extracorporeal system was used to administer isoflurane selectively into left anterior descending coronary artery (LAD) of in situ canine hearts (2).

Methods. After approval from our Institutional Animal Investigation Committee, studies were performed in five anesthetized (fentanyl-midazolam) and mechanically ventilated, open chest dogs. In each dog, LAD was cannulated and perfused via pressurized reservoir (100 mmHg) with isoflurane-free arterial blood (Control) and with arterial blood equilibrated in extracorporeal oxygenator with 1.4 % (1 MAC) isoflurane. CBF was measured with electromagnetic flowmeter. Aortic pressure, left ventricular end-diastolic pressure, left ventricular dP/dt max, and heart rate were measured. Data were obtained before and after 15 min, 1 hr, 2 hr, and 3 hr of intracoronary administration of isoflurane.

Results. Exposure to blood equilibrated with 1.4 % isoflurane caused initial five-fold increase in CBF (Fig 1), suggesting pronounced reduction in vascular resistance. CBF decreased progressively from this maximum, attaining level double control value after 3-hour exposure to isoflurane. Systemic hemodynamic parameters did not change during isoflurane.

Discussion. Isoflurane caused marked, initial coronary vasodilation. The vasodilation waned over time suggesting adaptation of coronary vascular smooth muscle to the relaxing effects of isoflurane. The phenomenon of time-dependent vascular adaptation may have contributed to variable increases in CBF observed in previous studies making measurements at different times during exposure to isoflurane (2,3).

References
1. Neurosurgery 14:135-141, 1984.
2. Anesthesiology 74:757-765, 1991.
3. Anesthesiology 66:273-279, 1987.

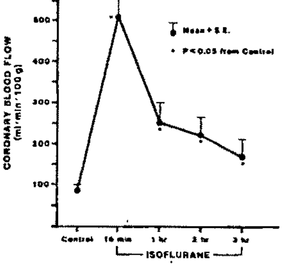

Fig 1. CBF during 3-hr exposure to isoflurane.

S61

TITLE:RELATIVE POTENCIES OF BARBITURATE ACTION AT THE *TORPEDO* ACETYLCHOLINE RECEPTOR ION CHANNEL

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INTRODUCTION: Despite wide daily use in anesthesia, the mechanism of action of barbiturates still remains uncertain. Possibilities include membrane perturbations and specific interactions with barbiturate sites/receptors. Because of the complexity of the C.N.S., barbiturate action is being studied at the neuromuscular junction.[1,2] Here we report the ion channel blocking potency for 13 barbiturates at the nicotinic acetylcholine receptor from Torpedo (AcChoR).

METHODS: The assay for inhibition of agonist induced cation flux has been previously described.[3] Briefly, the net efflux of $^{86}Rb^+$ was measured from sealed AcChoR rich membrane vesicles at 20°C during a 10-second exposure to agonist with and without a barbiturate.

RESULTS: The concentration-inhibition curve for each barbiturate was fitted to a logistic equation of the form:

$E = E_{max}\ [([B]_n)([B]^n+IC_{50}{}^n)^{-1}]$ where E is efflux, [B] is barbiturate concentration, n is Hill coefficient and IC_{50} is half-inhibition concentration. The IC_{50}s are given below and their average standard deviation was 20%.

Table 1. Relative Potencies of Barbiturates

Barbiturates	IC_{50},uM	IC_{50}/ED_{50}	%Occupancy at ED_{95}
Pentobarbital	32	0.20	0.96
Butabarbital	34	0.06	0.99
Thiopental	41	1.29	0.76
Butalbital	44	0.07	0.98
Secobarbital	48	0.58	0.88
Amobarbital	82	0.19	0.96
Methohexital	99	4.94	0.47
Aprobarbital	113	0.08	0.98
Mephobarbital	128	1.41	0.76
Hexobarbital	239	1.46	0.75
Metharbital	528	0.53	0.89
Phenobarbital	565	0.17	0.96
Barbital	877	0.06	0.99

DISCUSSION: All 13 barbiturates completely inhibited cation flux with IC_{50}s ranging from 30 to 900 uM. Pentobarbital and thiopental have nearly equal potencies in spite of differing in octanol/water partition coefficients (P). Generally, there is little relation between IC_{50} and P. This suggests that barbiturates act at a discrete site, an impression reinforced by the Hill coefficient being close to one. At the anesthetic concentration[2] barbiturate inhibition of the AcChoR's ion channel ranged from 47 to 99%. Interestingly, at their clinical concentrations thiopental and methohexital, the most potent of the commonly used barbiturates we studied, had amongst the least inhibitory action on the AcChoR. This is consistent with their causing little neuromuscular blockade under clinical conditions.

REFERENCES:1.Pharmacol Rev 24:583-655 (1972) 2.JPET 195:251-6 (1975) 3.Biochemistry 26:2807-2814 (1987)

S62

TITLE: INTERACTION OF BARBITURATES AND BENZODIAZEPINES AT THE $GABA_A$ RECEPTOR IN RAT BRAIN SYNAPTONEUROSOMES

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Combination of midazolam (diazepam) and pentobarbital (phenobarbital) has been found to result in a synergistic (supra-additive) hypnotic interaction both in humans and in rats (1,2). Attention has focussed on the $GABA_A$ receptor complex since both benzodiazepines and barbiturates interact with this complex. In addition, a strong positive correlation exists between anesthetic and GABA-mediated Cl^- uptake potencies for barbiturates (3). We have tested the hypothesis that supra-additive hypnotic interactions of benzodiazepines with barbiturates are due to a synergistic effect on Cl^- conductance subsequent to binding at allosterically coupled sites on the $GABA_A$ receptor complex.

$^{36}Cl^-$ flux and equilibrium binding measurements were performed using rat brain cerebrocortical synaptoneurosomes. All procedures involving animals were reviewed and approved by the Animal Use Sub-Comm., Univ. of AL at Birmingham. Studies from several laboratories have demonstrated the suitability of this vesicular model for measurement of GABA- or muscimol-mediated $^{36}Cl^-$ flux and recently we have demonstrated its suitability for equilibrium binding of [^{3}H]muscimol and [^{3}H]diazepam (4). Data for the effects of selected benzodiazepine and barbiturates and their combination on these parameters are collected in the table below. The benzodiazepines and barbiturates both allosterically enhance the binding of [^{3}H]muscimol to comparable, albeit modest, extents. The effect of these drugs on augmentation of muscimol-stimulated $^{36}Cl^-$ flux, however, is more robust and the barbiturates are more potent in this regard. Combination of benzodiazepine and barbiturate produces synergistic enhancement of [^{3}H]muscimol binding (Fig. 1), but, interestingly this is not reflected functionally by the enhancement of $^{36}Cl^-$ flux stimulation. Concentrations of barbiturates and benzodiazepines required for maximal stimulation of $^{36}Cl^-$ flux correlated nicely with concentrations of these drugs needed for maximal stimulation of [^{3}H]muscimol and [^{3}H]diazepam binding.

The positive cooperative interactions between benzodiazepines and barbiturates, as demonstrated behaviorally, may require a more complicated explanation then direct enhancement of Cl^- conductance resulting from an allosteric coupling between separate binding sites on the $GABA_A$ receptor complex and its chloride channel. This study was supported by NIH grant GM 39344 to I.Kissin.

References 1.) Anesthesiology 67:26-31, 1987. 2.) Anesth.Analg. 17:342-345, 1988. 3.) J.Pharm.& Exp.Therap. 238:763-768, 1986. 4.) Soc. for Neurosci. Abstr. 14:977, 1988; Submitted J.Neurochem. 1991.

Table 1: MAXIMAL STIMULATION^

Drug	$^{36}Cl^-$ flux Conc. (μM)	$^{36}Cl^-$ flux Stim. %*	^{3}H-muscimol binding Conc. (μM)	^{3}H-muscimol binding Stim. %	^{3}H-diazepam binding Conc. (μM)	^{3}H-diazepam binding Stim. %
GABA	50	270 ± 60	-----	-----	50	100 ± 4
Muscimol	100	250 ± 45	-----	-----	50	118 ± 4
Diazepam	$1^{\#}$	54 ± 11	1	18 ± 5	----	----
Midazolam	$1^{\#}$	42 ± 9	1	24 ± 8	----	----
Pentobarb.	$100^{\#}$	159 ± 14	200	18 ± 7	200	40 ± 8
Phenobarb.	$1000^{\#}$	106 ± 25	500	32 ± 10	1000	17 ± 3
Pento + mid	$100 + 1^{f}$	144 ± 26				
Pento + diaz	$100 + 1^{F}$	156 ± 62				
Pheno + mid	$1000 + 1^{\#}$	83 ± 12				

^ Data are the mean ± SEM of 3 experiments done in triplicate for binding and quadruplicate for flux.

[#] In the presence of 3 μM muscimol.

* Enhancement over $^{36}Cl^-$ flux levels produced by 3 μM muscimol alone.

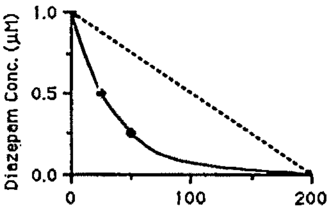

Fig. 1. Isobologram of enhancement of [^{3}H]muscimol binding. Diazepam (1 μM) and pentobarbital (200 μM) both potentiate [^{3}H]muscimol binding by 18 %. When combined together (solid line) the effect is supra-additve as demonstrated by the concave deflection away from the additive line (dotted line).

S63

TITLE: EFFECT OF MIDAZOLAM ON INDUCTION AND RECOVERY CHARACTERISTICS OF PROPOFOL
AUTHORS: J.A. DeLucia, D.O. and P.F. White, Ph.D., M.D.
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Outpatients frequently present for ambulatory surgery without the benefit of preanesthetic medication. Even the simple application of a face mask prior to induction of anesthesia can be an anxiety-provoking experience. We designed a randomized double-blind, placebo-controlled study to evaluate the perioperative effects of intravenous midazolam when administered as an adjuvant to propofol for co-induction of outpatient anesthesia.

75 healthy, consenting adults undergoing outpatient laparoscopy were randomly assigned to receive 5 ml iv containing either midazolam 2 mg, midazolam 5 mg, or saline, 5 min prior to induction of anesthesia according to an IRB-approved protocol. After fentanyl 100 ug iv, propofol was infused at a rate of 1 mg/kg/min to produce loss of consciousness. Maintenance of anesthesia consisted of a propofol infusion, 50-200 µg/kg/min, and nitrous oxide 67%. MAP, HR and SaO_2 were measured at 1-5 min intervals. Visual analog scales were used to assess the level of sedation and anxiety prior to and 3-5 min after the study drug. Data were analyzed using ANOVA and Chi-square testing, with $p<0.05$ considered significant. Values are means ± S.D.

The three treatment groups had similar demographic characteristics (table). Midazolam 2-5 mg iv, significantly increased sedation and decreased anxiety scores at the time of induction compared to pre-treatment values. Midazolam treated patients also had a significantly greater ↓MAP following induction and less ↑MAP with intubation than the saline group. Fewer patients in the midazolam groups recalled application of the face mask. In addition, 59% of the saline group recalled burning pain at the iv site during induction compared to only 16-33% in the midazolam groups. Although midazolam, 5 mg, iv prolonged emergence times, later recovery parameters were similar (table).

Midazolam 2-5 mg iv, produced sedation, anxiolysis and amnesia when administered to outpatients undergoing laparoscopy. In addition to decreasing the induction dose of propofol, midazolam attenuated the hemodynamic responses to tracheal intubation. While the higher dose delayed emergence from anesthesia, midazolam 2 mg produced similar beneficial effects during the induction period without altering the recovery profile. In summary, midazolam 2 mg iv is a useful adjuvant to propofol for co-induction of outpatient anesthesia.

TABLE	Control	Midazolam	
	Saline	2 mg	5 mg
Age (yr)	33±8	33±8	32±6
Weight (kg)	64±11	68±18	68±17
Surgery time (min)	52±18	58±26	62±38
Propofol induct. (mg/kg)	2.1±0.6	1.9±0.5	1.4±0.4*
maintenance (µg/kg/min)	154±54	143±41	125±38
Awakening (min)	5±2	5±2	7±4*
Extubation (min)	6±2	6±2	8±5*
Orientation (min)	7±3	7±3	11±6*
Standing (min)	80±30	84±36	83±25
Ambulating (min)	132±43	141±61	149±53
Discharge (min)	182±63	171±81	197±61

* Significantly different from the saline group, $p<0.05$. 2

S64

Title: Beta receptor antagonism does not fully explain esmolol induced Hypotension.
Authors: R. Deegan, M.D., A.J.J. Wood, M.D.
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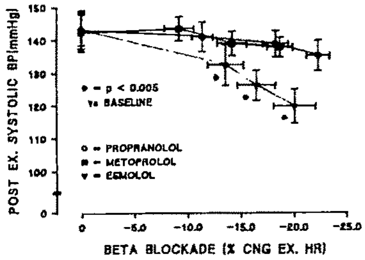
Introduction: Esmolol (E) is a β_1 antagonist used to reduce perioperative increases in heart rate (HR) and blood pressure (BP). Acute BP reduction occurs with E despite accepted dogma that I.V. ß blockade does not acutely affect BP. We therefore postulated that Esmolol may lower BP by mechanisms in addition to ß blockade(eg. vasodilation or sympathetic inhibition). To test this we compared the acute hypotensive, vascular and sympathetic effects of E, metoprolol (M) and propranolol (P) at equal degrees of ß blockade.

Methods: 9 healthy males were each studied 6 times with a week or more between studies. Each drug was administered twice: once to determine exercise (Ex) HR, pre- and post-Ex BP and plasma norepinephrine (NE); and again on a separate day for measurement of forearm blood flow (FBF) by strain-gauge plethysmography. Measurements were obtained pre-drug and during 3 infusion rates: E 6, 12 and 24 mg/min; P and M 20, 50 and 100 µg/min. ß-blockade was determined as % reduction in EX HR.

Results: Despite a similar range of ß-blockade with E, M & P, only E reduced post-Ex SBP (fig), with a maximum reduction of 23 ± 6 mmHg (p < 0 • 005). No change occurred in post-Ex DBP. E (but not P or M) also caused small reductions in pre-Ex DBP and MBP ($p<0.05$) at the intermediate & high doses. The greater BP reduction with E was not explained by vasodilation (FBF unchanged), or by sympathetic inhibition (Post Ex NE increased).

Discussion: This study therefore shows that E produces a hypotensive effect in excess of that seen with other ß blockers when administered to produce the same extent of ß blockade. This effect is most marked after exercise stress, a situation analogous to other stresses such as the perioperative state. The mechanism for the hypotensive effect of E remains to be defined, but is not explained by ß-blockade alone.



RELATIONSHIP BETWEEN β-BLOCKADE AND BLOOD PRESSURE.

S65

Title: EFFECTS OF GENERAL ANESTHETICS AND RELAXANTS ON IMMEDIATE AND 24 HOUR CPK LEVELS IN CHILDREN

Authors: SK Dhandha MD, P Kerkar MD, and MR Jewell MD

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Introduction: Intramuscular injections and intravenous succinylcholine are known to cause increases in blood CPK values. Halothane exacerbates the amount of CPK released from the skeletal muscle cells in children secondary to rhabdomyolysis.(1) The object of this study was to compare the influence of halothane (hal), isoflurane (isofl), IM methohexital (meth), succinylcholine (sch) and vecuronium (vec) on immediate and 24 hour postop CPK levels in pediatric patients. Inductions were by inhaled halothane or isoflurane or by IM methohexital.

Methods: Fifty-nine general surgical patients, age 1 to 13 years, were selected for their anticipated minimal muscle trauma and their normal preop CPK values. Of the 38 who received halothane, Grp. I (6) had meth. and sch.; Grp. II (13) had meth. and vec.; Grp. III (12) had sch., and Grp. IV (7) had vec. Of the 21 receiving isoflurane, Grp. V (8) had sch. and Grp. VI (13) had vec. In the venous blood samples collected preop, immediate postop, and 24 hours postop, CPK values of 25-350 U/L were considered as normal, 350-750 as increased, and over 750 as high (multiple point rate test).

Results: As shown in Table 1.

Table 1. Summary of CPK Levels in %

			Immed post			24 hr post		
Grp	Pts	Agents	Nml	Incr	Hi	Nml	Incr	Hi
I	6	hal/meth/sch	67	17	17	0	17	83
II	13	hal/meth/vec	46	39	15	15	31	54
III	12	hal/sch	75	17	8	25	25	50
IV	7	hal/vec	86	0	14	72	14	14
V	8	isofl/sch	100	0	0	63	37	0
VI	13	isofl/vec	100	0	0	54	15	31

Discussion: Both the release of intracellular CPK and the rhabdomyolysis associated with succinylcholine and halothane were very significantly reduced when isoflurane was used. The vecuronium versus succinylcholine comparisons did not produce as largely significant differences. As expected, IM administration resulted in raised values.

References: (1) Japanese J of Anes, 39(9), 1198-205, 1990.

S66

MAXIMUM ACCELERATION OF PULMONARY BLOOD FLOW AND RIGHT VENTRICULAR PERFORMANCE IN THE DOG

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Introduction: After cardiac transplantation, right ventricular (RV) dysfunction is a major cause of morbidity and mortality. Maximum acceleration of blood flow (A-max) measured in the aorta has been shown to provide information about left ventricular performance.[1,2,3] If these findings are applicable to the RV, A-max may be useful in evaluating RV performance in transplant recipients. Our purpose, therefore, was to show the effect of changes in loading conditions and contractility on A-max in a model of acute pulmonary hypertension.

Methods: Six mongrel dogs (20-25kg) were anesthetized with fentanyl and diazepam and mechanically ventilated. Catheters were inserted to determine systemic blood pressure (BP), central venous (CVP) and pulmonary artery (PAP) pressures, and cardiac output (CO). An ultrasonic flow probe was placed around the main pulmonary artery through a midline sternotomy to measure blood flow velocity (PAv). A left atrial catheter was inserted for pressure monitoring (LAP) and drug infusion. Pacing wires were attached to the right atrial appendage to control heart rate (HR).

Measurements of HR, BP, CVP, PAP, LAP, CO, and PAv were obtained at baseline and after increasing contractility (dobutamine 10µg/kg/m), perfusion pressure (phenylephrine to a 30% increase in BP), preload (hetastarch, 500ml), and HR (pacing rate increased 30%). The same series of measurements were repeated after a doubling of mean PAP brought about by the injection of glass beads (60-80µm diam.) into the central venous circulation.

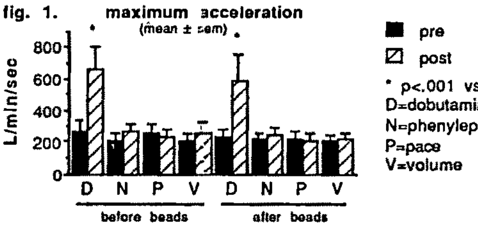
Statistical significance ($p<.05$) was determined by two way analysis of variance and Tukey's procedure.

Results: Dobutamine resulted in a significant increase in both A-max (maximum dPAv/dt) and stroke volume (SV) before and after beads [fig. 1]. Volume loading resulted in a similar increase in SV but no increase in A-max. Pacing and phenylephrine did not change A-max. The infusion of glass beads resulted in a two-fold increase in pulmonary vascular resistance and was not associated with any change in A-max, nor did it alter the effect of the four interventions on A-max.

Discussion: The present study suggests that A-max of pulmonary blood flow is a load and rate independent indicator of RV contractility. Monitoring A-max may be useful in the assessment of RV performance in the setting of acute pulmonary hypertension.

1. Circ. 74:323-329, 1986 2. Circ. 74:181-186, 1986
3. Anes. 69:728-737, 1988

fig. 1. maximum acceleration



S67

TITLE: USE OF KETOROLAC AND DEZOCINE AS ALTERNATIVES TO FENTANYL DURING OUTPATIENT LAPAROSCOPY

AUTHORS: Y. Ding, M.D., R. TerKonda, M.D., P. F. White, Ph.D., M.D., F.F.A.R.A.C.S.
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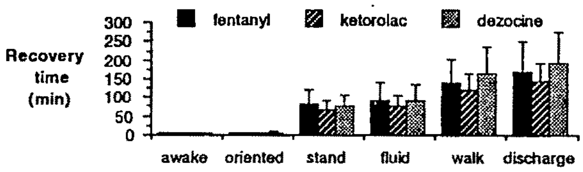
Opioid and non-opioid analgesics are widely used as adjuncts during outpatient anesthesia. Dezocine (Dalgan®), a partial opioid agonist, and ketorolac (Toradol®), a non-steroidal anti-inflammatory drug, are parenteral analgesics which have recently been approved for clinical use in the United States. We designed a randomized, double-blind study to compare dezocine and ketorolac to fentanyl during outpatient laparoscopy. We evaluated intraoperative conditions, recovery times and side effect profiles.

120 consenting adult female outpatient undergoing laparoscopic procedures were randomly assigned to one of three treatment groups according to an IRB-approved protocol. All patients received 2 ml of study drug (1 ml iv and 1 ml im) containing either dezocine, 6 mg, ketorolac, 60 mg, or fentanyl, 100 µg. A standardized general anesthetic technique consisting of midazolam 2 mg, fentanyl 50 µg, and propofol 2 mg/kg for induction, followed by propofol 120 µg/kg/min, vecuronium 1-2 mg/kg, and nitrous oxide 67% in oxygen for maintenance was used. At the end of surgery, the propofol infusion and N_2O were discontinued. Recovery times and postoperative side effects were recorded. Sedation, anxiety, pain, and nausea were assessed before and after the operation using visual analog scales. Data were analyzed using ANOVA for continuous variables and Chi-square test, with $p<0.05$ considered statistically significant (mean values ± S.D.).

The three treatment groups were compared with respect to demographic data. Hemodynamic changes during induction and maintenance of anesthesia, as well as recovery times were similar (fig. 1). In the PACU, 78% of the control patients complained of pain, compared to 38% with dezocine and 41% with ketorolac. Similarly, less postoperative fentanyl was required in the dezocine (16±35µg) and ketorolac (18±30µg) groups compared to the control group (62±77µg). However, patients receiving dezocine had a higher incidence of postoperative nausea (62%) than the fentanyl (22%) or ketorolac-treated (15%) groups.

Ketorolac and dezocine were effective alternatives to fentanyl when administered during outpatient laparoscopy. However, dezocine was associated with an increased incidence of postoperative nausea and vomiting.



S68

Title: EVALUATION OF THE EFFICACY AND SAFETY OF IV PREMEDICATION FOR DENTAL OUTPATIENTS

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Affiliation: National Institute of Dental Research, NIH, Bethesda MD, [1]UCLA, Los Angeles, CA, [2]Univ. Pittsburgh, Pittsburgh PA, [3]Univ. North Carolina, Chapel Hill NC, [4]Univ. Kentucky, Lexington KY, [5]Univ. Washington, Seattle WA

Introduction: The clinical efficacy and physiologic effects of prototypic drug regimens administered intravenously for premedication was evaluated in ambulatory patients undergoing oral surgery to characterize the relationship between safety and efficacy in this patient population.

Methods: A multicenter, parallel groups, double-blind clinical trial was conducted at five sites in patients undergoing oral surgery with intravenous premedication and local anesthesia. A total of 997 patients were randomly allocated to receive one of five treatments: placebo (PL), midazolam (M) titrated to slurring of speech and patient report of relaxation without loss of consciousness (mean dose = 8.6 mg), 1.4 micrograms/kg fentanyl plus midazolam (mean dose = 5.7 mg) titrated to the same endpoint (M+F), midazolam titrated to the same endpoint plus additional midazolam (mean total dose = 16.7 mg) as needed during the procedure (M+M), or 1.4 micrograms/kg fentanyl plus midazolam (mean dose = 5.8 mg) titrated to the same endpoint with methohexital (mean dose = 69.7 mg) as needed during the procedure (M+F+Mx). Blood pressure (BP), heart rate (HR), respiration rate (RR), O_2 saturation, expired CO_2, patient self report of efficacy, and surgeon and observer ratings of efficacy were collected prior and during drug administration, intraoperatively, and up to 90 min post drug. Data were analyzed by one-way analysis of variance with pair-wise comparisons or Pearson's chi-square.

Results: All five groups were similar in baseline BP, HR, RR, age, sex, ASA class, and anxiety state and trait. The mean duration of oral surgery (24.9 min), the type of surgical extractions, and the surgeons' estimate of trauma were also similar across groups. Administration of M+F and M+F+Mx resulted in a significant decrease in O_2 saturation ($P<0.01$), RR ($P<0.01$), and elevated CO_2 ($P<0.01$) which persisted up to 5 mins intraoperatively. No difference was seen in BP or HR in any groups compared to PL during surgery. O_2 saturation, RR, and expired CO_2 remained similar to PL in the M and M+M groups. All treatments significantly reduced intraoperative anxiety with less discomfort reported intraoperatively following M+F+Mx ($P<0.01$). The efficacy of sedation was rated by the oral surgeons as significantly better than PL for all treatments with M+F+Mx rated as significantly better than M ($P<0.01$), M+M ($P<0.01$), and M+F ($P<0.05$). Patient cooperation during the procedure was improved by M+F and M+F+Mx ($P<0.01$) in comparison to placebo. Patients' global evaluation was significantly better than PL for all treatments with M+M and M+F+Mx judged most effective. Amnesia to pictures shown during the procedure and to actual clinical events was also greatest for M+M and M+F+Mx. Decreasing the midazolam dose to permit administration of fentanyl resulted in greater recall.

Discussion: Intravenous premedication is used as an alternative to general anesthesia for ambulatory outpatients on the assumption that is effective yet safer. The results of this large sample indicate that administration of a benzodiazepine results in reduced anxiety, amnesia to noxious clinical procedures, and high patient acceptance with no detectable physiologic impairment. The addition of an opioid or an opioid plus a barbiturate produces greater CNS depression resulting in a more cooperative patient but with transient respiratory depression. The results indicate that these drug classes are safe and efficacious when slowly titrated by appropriately trained dentists to carefully monitored patients.

S69

Title: INFLUENCE OF HEMOGLOBIN ON MYOCARDIAL LACTATE FLUX IN PATIENTS UNDERGOING CORONARY BYPASS

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Introduction: Increasing concern over complications related to blood transfusions has prompted a re-evaluation of what constitutes an "adequate" hemoglobin concentration (HGB) particularly in patients undergoing coronary artery bypass graft (CABG) surgery who may be at risk for myocardial ischemia. In this study, we examined the effect of HGB on myocardial lactate flux (MLF), as a measure of ischemia, in 195 CABG patients.

Methods: Data from 195 patients who had undergone CABG and participated in clinical studies at our center since 1982[1,2,3] were re-examined to determine the relationship between MLF and HGB. MLF was calculated as the product of arterial-coronary sinus lactate difference and coronary sinus blood flow measurements. Simultaneous HGB values were recorded. A total of 1598 data points were collected representing measurements taken from the time of insertion of the coronary sinus catheter prior to induction of anesthesia until just prior to the onset of CPB, and from the time of separation from CPB until up to 24 hours post-operatively. A multiple stepwise linear regression technique (SYSTAT, Systat, Inc.) determined the interaction between MLF, HGB, and hemodynamic variables.

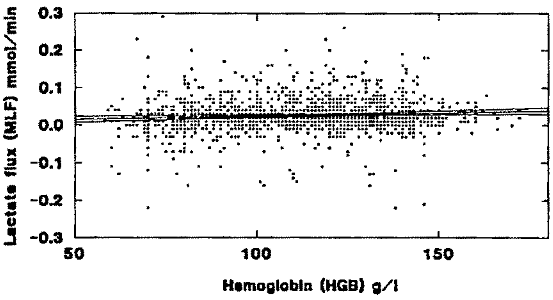
Results: The Figure shows a scatter diagram of the 1598 points plotted as MLF vs HGB, including the regression line and 95% confidence interval. The equation for the line was $MLF = 0.0071 + (2*10^{-4}) * HGB$ with the slope being highly significant ($p < 0.001$), however the adjusted squared multiple R (R^2) was only 0.008. Multiple regression analysis did not reveal HGB to be a significant independent term affecting MLF.

Discussion: This retrospective evaluation of the association between HGB and MLF suggests that, based on the slope of the line (Figure), within the range of HGB measured (58 - 172 g/l) there is no clinically significant relationship between MLF and HGB. The very low R^2 (0.007) suggests over 99% of the variability in MLF is attributable to factors other than HGB. Weisel et al.[4] measured lactate extraction in 14 post-operative CPB patients in whom crystalloid fluid replacement produced mean HGB values of 89 g/l, and concluded that, in the early post-operative period, a normal lactate extraction can only be obtained with a HGB value greater than 100 g/l. Our data does not support this, and in fact suggests HGB as low as 60-70 g/l in the perioperative period is not associated with a clinically significant change in MLF.

References:

1. Bailliere's Clinical Anesthesiology 1989; 3:27-46
2. Can J Anaesth 1991; (In press)
3. Can J Anaesth 1991; 38:A22
4. J Thorac Cardiovasc Surg 1989; 88:26-38

Figure. Myocardial lactate flux vs Hemoglobin concentration in 195 patients (1598 data points).



S70

ISOFLURANE INCREASES DEFIBRILLATION THRESHOLD IN MAN

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Introduction:

Implantation of Pacemaker-Cardioverter-Defibrillator (PCD) devices is increasingly used for the treatment of drug refractory malignant tachyarrhythmias.[1] Assessment of the defibrillation threshold (DT) is commonly done under general anésthesia, however, the effects of volatile agents on DT of the human heart are unknown since only the influence of inhalational agents on DT in animals has been reported.[2] This study investigated the effect of Isoflurane on the DT in a group of patients undergoing evaluation for PCD implantation.

Methods:

After institutional review board approval, five patients aged 52-64 were studied. Anesthesia was induced with Midazolam 0.2mg/kg, Vecuronium 0.2mg/kg and Alfentanil 30μg/kg, and maintained with increments of Midazolam and Alfentanil. To monitor the depth of anesthesia an Anesthetic Agent Monitor 222, Puritan Bennet was used. After insertion of an endocardial multipolar catheter, ventricular fibrillation was induced by rapid ventricular pacing, then a defibrillation shock was applied. DT was determined as the lowest energy (in Joules) which terminated ventricular fibrillation. 1MAC (end-tidal volume %-1.4) Isoflurane was then administered and the defibrillation protocol repeated. Paired t-test was used to analyze data.

Results: DT increased significantly ($p<0.05$) after 1MAC Isoflurane, ranging from 20-75% (Table).

Discussion: The increase in DT we observed during 1MAC Isoflurane was greater than that reported in dogs.[2] These results suggest that Isoflurane administration can influence determination of DT in patients undergoing PCD implantation and could impair defibrillative function of PCD.

References:

1. N Deutsh et al, "Perioperative Management of Patients Undergoing Automatic Internal Cardioverter-Defibrillator Implantation", J. of Cardioth. Anes., 14:236-244, 1990.
2. EC Speck et al, "Effect of Volatile Anesthetics on Defibrillation Threshold in Dogs", Anes., 63:A87, 1985.

Table:

Patient	DT(Joules)	1MAC Isofl. DT(Joules)	% Increase
1	10	14	40
2	12	16	33
3	8	14	75
4	10	12	20
5	8	12	50
Mean±SD	9.6 ± 2.8	13.6 ± 2.4*	43.6 ± 16.4*

* p<0.05 DT-defibrillation threshold

S71

Title: EFFICACY OF INTRATHECAL MORPHINE FOR POSTOPERATIVE ANALGESIA IN A SMALL COMMUNITY HOSPITAL

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Affiliation: Department of Anesthesia Botsford General Hospital, Farmington, MI

Introduction: Due to the limited resources available in community hospitals, methods of postoperative pain control must provide adequate analgesia and must be safe and simple to manage. In this prospective study we examined the routine use of intrathecal opioids in a community hospital.

Methods: All patients having abdominal or lower extremity orthopedic procedures were considered for inclusion in this IRB-approved protocol. Selection criteria required the patients written informed consent. Commercially available preservative-free morphine (0.3 mg) was used in all patients. No attempts were made to alter the intraoperative anesthetic technique. When general anesthesia was chosen the morphine was diluted to a total of 1 ml with CSF and injected just prior to induction. When spinal anesthesia was chosen the morphine was added to the local anesthetic solution. After surgery and stabilization in the recovery room the patient was sent to the general floor. Morphine was given intravenously when the patient complained of pain. The interval from the injection of intrathecal morphine to the request for analgesia was noted. An ampule of Naloxone with a syringe was kept at the patients bedside for 24 hours. Standing orders included documentation of vital signs at hourly intervals for 24 hours post intrathecal injection and treatment protocols for side effects including pruritus, nausea, vomiting, and urinary retention. Respiratory depression was defined as a respiratory rate of less than 10 breaths/min and somnolence as judged by the nursing staff.

Results: 200 patients, ASA physical status I to III were included in this study (111 abdominal/ 89 orthopedic). 63% of the abdominal surgery patients and 52% of the orthopedic surgery patients did not require any analgesia for pain relief in 24 hours. An isolated respiratory rate of less than 10/min was seen in two patients; both were alert and required no treatment. Pruritus was the most common side effect. It occurred in a total of 42% of the patients.

Discussion: We have shown that with properly trained floor nurses the risk of delayed respiratory depression leading to serious sequelae is rare, and that intrathecal morphine can be an effective, safe, and simple method for postoperative pain control in a community hospital.

S72

Title: PREDICTORS OF SELF-EXTUBATION IN AN URBAN TRAUMA CENTER

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Introduction: Although endotracheal intubation is a common occurrence in the critical care unit, there is a paucity of literature regarding one of its most life-threatening complications, self-extubation (SXT). We retrospectively evaluated the incidence, clinical features, and outcomes of SXT in our Multi-Trauma Unit.

Methods: Our Trauma Registry was used to identify all mechanically ventilated patients with SXT listed as a complication. We then reviewed the medical records of these patients for variables that may have contributed to this event.

Results: In a 12 month period, 584 mechanically ventilated patients (Male-421; Mean Age 39.9 + 19.5 yrs) were admitted. Eighty-one SXTs occurred in 73 patients: a 13.9% incidence. Nine of the SXTs (11%) appear to have been accidental while the other 72 appear to have been secondary to patient effort. Mean intubation period before SXT was 7 days. A disproportionate number (64.2%) of SXTs occurred between the hours of 7pm and 7am. The nurse to patient ratio remained the same during all shifts. Ninety-one percent of the self-extubated patients received intravenous sedation within 4 hours of the event, and 54% of the patients were restrained. None of the patients received muscle relaxants. There was a significant difference in the number of patients with a diagnosed head injury (GCS<12 and CAT scan confirmed) in the SXT group when compared to the non-SXT group (56.8% vs 43.7% respectively p<.03). Of the eight patients that extubated themselves twice, 5 had head injuries, and fourteen of the sixteen SXTs in this group occurred between the hours of 7pm and 7am. Finally, 59.2% of the SXTs required re-intubation for respiratory depression that was clinically evident within 30 minutes. Only one patient developed an arrhythmia with associated hypotension post SXT.

Discussion: Our experience suggests that:
1) SXT is more likely to occur between the hours of 7pm and 7am.
2) SXT is more likely to occur in patients with a diagnosed head injury.
3) the majority of SXT patients will require re-intubation for respiratory insufficiency.
4) although SXT is a serious complication, it can be managed safely with few negative sequelae.

S73

Title: FACTORS INFLUENCING HEPATIC ARTERY BLOOD FLOW IN THE HUMAN TRANSPLANTED LIVER

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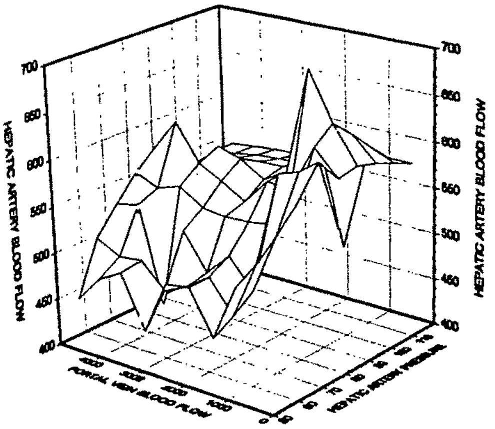
Introduction: The phenomenon of portal vein flow control of hepatic artery resistance is well known, but poorly understood. Patients presenting for orthotopic liver transplantation (OLT) often have portal hypertension that resolves when a graft liver with normal portal resistance is implanted. However, the result is a dramatic increase in portal vein flow (PVF) which increases hepatic artery resistance (HAR), and in a subset of patients decreases hepatic arterial flow (HAF) below that required for graft survival or optimal performance. The purpose of this study was to identify other variables that could influence HAF. This retrospective review examines the relationship between HAF, systemic arterial pressure (MAP), and PVF during OLT.

Methods: A retrospective review of 139 patients undergoing OLT between 2/1/90 and 4/24/91 with complete data were examined. HAF and PVF (electromagnetic flow probes); systemic, portal and hepatic vein pressures; and cardiac output were recorded at least 1 hour following complete reperfusion of the graft liver. In patients with low HAF, the portal vein was clamped intermittently and/or papaverine was injected directly into the hepatic artery in an attempt to improve blood flow.

Results: When the portal vein was clamped for 10 to 15 seconds the HAF typically increased but returned to previously low levels when the portal vein was unclamped. Patients receiving papaverine also only had transient increases in HAF. However, as illustrated in the figure, when the MAP was low and the PVF was high the HAF was at the lowest levels.

Discussion: Typically patients presenting for OLT have low MAP. A subset of OLT patients exist in whom HAF is unacceptably low resulting in graft failure, extremely slow return of hepatic function or a clotted hepatic artery. In these patients with low HAF and very high PVF the systemic pressure may not be adequate to overcome the HAR. Data from our isolated perfused porcine liver model demonstrated that HAR is a function of both HAF and PVF (HAR decreasing with increasing HAF and decreasing PVF). Under constant pressure perfusion the HAR becomes so high during low perfusion pressures and high PVF that the HAF diminishes to a few ml/min. These findings are consistent with our retrospective review of patient data. As intraoperative interventions result in only transient improvement in HAF, other treatment modalities aimed at improving and maintaining MAP should be sought to improve graft performance and the likelihood of graft survival.



S74

TITLE: A COMPARISON OF ORAL NALTREXONE TO INTRAVENOUS NALOXONE FOR PREVENTION OF EPIDURAL MORPHINE SIDE EFFECTS AFTER CESAREAN SECTION

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INTRODUCTION: The use of oral naltrexone for prevention of epidural morphine side effects has been previously reported[1,2]. However, its efficacy and safety in a large number of patients as well as a comparison to an alternate method (intravenous naloxone) has not been described.

METHODS: With the approval of our Institution Review Board, 271 patients undergoing Cesarean section were studied over a 6 month period (3 months for each group) comparing a continous intravenous infusion of naloxone (160 micrograms/hour) to a single oral dose of naltrexone (3 milligrams). Epidural morphine was given at cord clamp through a low lumbar epidural catheter and the prophylactic drug was begun when the patient entered the recovery room.

Data was obtained retrospectively by reviewing quality assurance records collected on each patient during her hospitalization. A positive response for a side effect (breakthrough pain, nausea, pruritus or respiratory depression) was noted when drug treatment was given for that side effect. Patients were asked on postoperative day one if they were satisfied with the form of pain control they received. Statistical analysis was performed using a Chi-Square for categorical data and a Students t-test for numerical data. A p value of less than .05 was considered statistically significant.

RESULTS: There was significantly less pruritus in the oral naltrexone group; otherwise there were no differences between the groups. Although statistically significant, the duramorph dose was only slightly larger in the oral naltrexone group.

	ORAL (n=144)	IV (n=127)	p VALUE
DURAMORPH DOSE (MG)	4.68 ± 0.47	4.55 ± 0.45	< .017
BREAKTHROUGH PAIN	55.6%	62.2%	NS
HOURS TO BREAKTHROUGH	4.37 ± 5.73	5.24 ± 5.64	NS
PRURITUS	25.7%	40.2%	< .012
NAUSEA	6.3%	9.5%	NS
RESPIRATORY DEPRESSION	0.7%	0%	NS
PATIENT SATISFIED	98.6%	97.6%	NS

TABLE 1. Results are shown as mean values plus or minus standard deviations or as the percentage of patients with a positive response.

DISCUSSION: Plasma levels of morphine peak within one hour after epidural administration, yet side effects due to rostral spread occur hours after its metabolism[3]. Naloxone has primary antagonist activity with a plasma half-life of only one hour[4]. It is thus desirable to use a long acting pure narcotic antagonist such as oral naltrexone which has been shown to provide effective anatagonism for up to 24 hours[5].

Oral naltrexone (3mg) is a simple, effective and safe prophylactic treatment for epidural morphine side effects after Cesarean section and may be more effective than low dose (160 micrograms/hour) intravenous naloxone for pruritus prevention. This therapy is also cost effective, saving approximatelly $14,000 per year in material costs alone when compared to intravenous naloxone at our institution.

REFERENCES: 1. Anesthesiology 72:233-237, 1990 2. Anesthesiology 65:A200, 1986 3. Br. J. Anesth 54:843-847, 1982 4. Factors Affecting the Action of Narcotics, Raven Press 297-343, 1978 5. Am J. Psychiatry 131:646-650, 1974

Special thanks to the Acute Pain Service nurses (Susan Myers, Carol Perry, and Carol Taylor) for their assistance in this study.

S75

INDUCTION OF C-FOS PROTEIN IN RAT STRIATUM BY COCAINE. C.L. Duncan, H.E. Criswell, G. Duncan, L. Grimes, G.R. Breese and R.A. Mueller. Depts. of Anesthesiology, Psychiatry, Cell Biology, and Pharmacology, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC 27599.

Cocaine, like other local anesthetics, can produce central excitatory effects with overdosage. In addition, recreational use produces both a euphoric or psychostimulant response and an enhanced response to subsequent drug exposure. The mechanisms responsible for this behavioral sensitization are thought to involve CNS dopaminergic pathways. The current study sought to examine if cocaine administration to rats in a repeated dosage (10 day) paradigm known to produce behavioral potentiation altered the expression of the immediate-early gene c-fos. Positive staining for the protein of this proto-oncogene would pinpoint which neuronal cell population in the dopamine-rich stratum is involved in the response to cocaine, as well as begin to uncover the genetic basis of the sensitization.

Rats were perfused with 4% paraformaldehyde and 0.2% glutaraldehyde and 30 Vibratome sections of brain tissue were immunohistochemically stained for c-fos protein. The striatum was divided into medial, central, and lateral areas and the stained nuclei counted.

Counts of c-fos positive nuclei in the striatum 2 hours after cocaine (10 mg/kg to 60 mg/kg i.p.), revealed a dose-response curve with maximal expression at 40 mg/kg. There was no c-fos expression observed in the saline controls. In all cocaine treated rats there was a marked medial to lateral striatal anatomic gradient of stained nuclei. Pretreatment with the specific D_1 antagonist SCH23390 (0.5 mg/kg) completely blocked the striatal c-fos response to cocaine 40 mg/kg.

The D_2 antagonist haloperidol (0.5 mg/kg) alone induced marked c-fos staining throughout the striatum, however, pre-treatment with haloperidol markedly attenuated the response to cocaine 40mg/kg. Repeated daily administration did not alter the number of c-fos positive cells on subsequent re-exposure.

These results suggest that activation of the immediate-early gene c-fos in striatal post- synaptic cells which contain D_1 dopamine receptors may play a role in the behavioral changes produced by cocaine administration. Secondly, the enhanced degree of behavioral activation with repeated dosing is not accompanied by enhanced c-fos immunoreactivity, and thus the proto-oncogene may be limited to accommodation of the cell to drug exposure rather than simply a part of the general activation seen with psychostimulant administration.

S76

Title: ARE ANESTHETIC COMPLICATIONS PREDICTABLE IN DAY SURGICAL PRACTICE?
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Introduction: We questioned if the preoperative patient evaluation allows prediction of adverse outcomes in day surgery.

Methods: After ethics approval all adult patients in four Canadian hospitals, had recorded data on demographics, medical illness, and other factors. The anesthetic and surgical procedure, as well as events in the intraoperative (OR) or recovery periods (RR) were described. The study featured parallel hospital methodology, trained research nurses, and standardized outcome definitions. The crude rates of adverse events were determined for day surgical cases (defined as no postoperative stay); since rates were low, like outcomes were grouped. Adjusted relative odds using multiple logistic regression were then calculated for each preoperative medical illness.

Results: There were 6,914 day surgical patients (general or regional anesthetic). The crude rates varied, but no single outcome occurred in greater than 1%. With the exception of nausea and vomiting, 98% of patients had no incident. There were no postoperative deaths, and three patients were admitted. When preoperative illness are evaluated it was found that cardiorespiratory disease predicted OR (but not RR) events. G.I. diseases predicted BP and lower respiratory problems, while diabetics were at risk for surgical bleeding. The obese had higher risks whereas smokers had reduced risks, especially of nausea/vomiting.

Conclusion: The low incidence of events supports the safety of day surgery. However, patients with preoperative illnesses, (even judged to be under control) were at higher risk.

Table: Adjusted Relative risks (*P≤0.01).

	OR	RR
COPD	2.2*	0.8
MI < 6/12	6.4	3.0
↑ BP	2.2*	1.3
CHF	2.7	1.3
GI	2.7*	1.1
Renal	0.7	1.9
Diabetes	1.6	1.6
Neurologic	1.4	1.2
Diff airway	3.5*	1.8
Full stomach	1.6	1.2
Obesity	1.9*	1.4*
Smoker	1.2	0.8

S77

Title: DIAGNOSTIC AND THERAPEUTIC BRACHIAL PLEXUS BLOCK FOR RSD UNRESPONSIVE TO STELLATE GANGLION BLOCK

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Introduction: In the occasional patient presenting with the "classical" signs and symptoms of reflex sympathetic dystrophy (RSD) of the upper extremity who fails to obtain relief from a series of stellate ganglion blocks, it has been our practice to carry out a differential brachial plexus block before accepting the fact that our clinical impression was incorrect. The present paper describes the results of differential brachial plexus blocks in 25 patients.
Methods: In 25 patients with "obvious symptoms of RSD" who failed to obtain relief from a series of stellate ganglion blocks, differential brachial plexus block was carried out using the axillary perivascular, subclavian perivascular, or interscalene technics, though the latter technic was used in the majority of cases using mepivacaine 1.5%. If the differential block indicated a sympathetic mechanism, a series of therapeutic blocks were carried out.
Results: Nineteen of the 25 patients (76%) subjected to differential brachial plexus blockade had a response indicative of a sympathetic mechanism. Two of the 25 (8%) had a response indicative of a somatic mechanism, while 4 (16%) had a response indicative of a "central" mechanism. Of the 19 patients shown to have sympathetic pain, 12 patients (63%) had long-term pain relief following a series of therapeutic brachial plexus block, while 7 patients (37%) only had temporary relief.
Discussion: In some patients, sympathetic fibers leave the sympathetic chain well below the stellate ganglion, join the second and third thoracic nerves, and enter the brachial plexus by means of a branch to the first thoracic nerve (the nerve of Kuntz), thus totally bypassing the stellate ganglion(1). Therefore, it is possible that the local anesthetic solution injected at the level of the stellate ganglion may fail to dissect far enough caudally to reach those fibers which leave the sympathetic chain at the level of the second or third thoracic ganglia. Because the perivascular technics of brachial plexus block block all of the sympathetic fibers to the arm, it would appear that brachial block may be superior to stellate ganglion block for the diagnosis and management of RSD of the upper extremity.

References:
1. Archives of Surgery 15:871-877, 1927

S78

Title: DOES PROPOFOL HAVE ANALGESIC PROPERTIES?

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Goodman D, BS,
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INTRODUCTION: To explore the possible analgesic effects[1,2] of propofol, the analgesic requirements of three groups of patients were compared. One group received TIVA with propofol (P) as the sole agent. The other groups received propofol and fentanyl (F).
METHODS: With IRB approval, and written, informed consent, 62 patients aged 18-55 years presenting for lower abdominal or orthopedic surgery were enrolled into the study. Patients were assigned at random to one of three groups: A (P as sole agent), B (P at a constant concentration and F varied), C (F at a constant concentration and P varied). Both P and F were administered using CACI[3], (a pharmacokinetic model driven infusion device) to preset blood concentrations. In group A anesthesia was induced and maintained with propofol. In group B an infusion of P (to 2.5μg/ml) and in group C an infusion of F (to 1.5 ng/ml) was started 3 minutes before induction. Group B patients were induced with F and Group C patients with P. All patients were ventilated to normocapnia with oxygen. After incision, P or F was titrated to give adequate anesthesia: Every 15 minutes, if the patient showed no response to surgery, the concentration of P (Groups A,C) was reduced by 0.5μg/ml, or the concentration of F (Group B) was reduced by 0.5ng/ml. Hemodynamic, somatic, or autonomic response to surgery was treated by up to 3 set increases in the concentration of P (Groups A,C) or F (Group B). Inadequate anesthesia after a third increase was treated by increasing the fixed agent (Groups B,C) or by giving F (Group A), and these patients were excluded from the analysis. The infusions were stopped at the end of surgery, and the recovery times were recorded. In the PACU, patient controlled analgesia with an iv opioid was started. The opioid requirements (morphine equivalent) for 24 hours after operation were recorded. ANOVA was used to compare differences between groups. $p<0.05$ was considered significant.
RESULTS: The table shows mean propofol concentrations during surgery, recovery times (minutes) and opioid requirements. There were no significant differences in opioid requirements for the first four hours whether or not fentanyl was used. Recovery was significantly longer in Group A patients.
DISCUSSION: High blood concentrations are needed when propofol is used as a sole anesthetic agent. This results in a prolonged recovery time during which the analgesic requirements are the same as in patients who have received significant amounts of fentanyl intraoperatively. This suggests that propofol has analgesic properties at sedative concentrations.

References: 1 British Journal of Anaesthesia 54: 307 1982; 2 Seminars in Anesthesia VII: 4-20 1988;
3 Anesthesiology 73: 1082-90, 1990.

Mean±SEM	Group A (n=22)	Group B (n=18)	Group C (n=22)
Protocol success	15	10	21
Propofol conc (μg/ml)	9.4±0.4	2.5 (pred)	3.4±0.2
Time to orientate	34.4±4.8*	18.2±4.7	15.6±3
Respond to command	26.7±5.3*	8.6±0.8	11.7±2
Morphine (mg) 0-1hr	4.2±1.1	2.3±1.3	6±1.5
Morphine 1-2 hr	5.1±1.5	3.6±1	5.8±1.8
Morphine 2-4 hr	10.4±1.8	7±1.2	6.5±1.6
Morphine 4-24 hr	57±8.8	27±4.9	41±7.1

*$p<0.05$ A vs B and C

S79

TITLE: THE EFFECT OF AUTOMATIC RECORD KEEPING ON VIGILANCE AND RECORD KEEPING TIME

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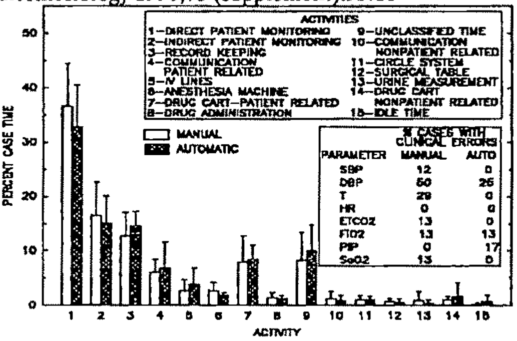
Proponents of intraoperative automatic anesthesia record keepers (AARK) profess that this new technology decreases record keeping time, leaving more time for data interpretation[1]. Critics state that the AARK takes the anesthetist out of the information feedback loop which may reduce patient vigilance[2]. In this paper we report results from an ongoing study which examines these claims.

With informed consent and institutional approval we videotaped the attending anesthetist and the immediate surroundings during 22 surgical procedures. In eleven cases, the anesthetist charted the intraoperative record manually; in the remaining procedures, he/she used an AARK (ARKIVE, Diatek). Once during each case, an examiner entered the operating room unannounced and asked the anesthetist to turn away from the monitors and recall the patient's current systolic pressure (SP), diastolic pressure (DP), heart rate (HR), end-tidal carbon dioxide ($ETCO_2$), inspired oxygen (FiO_2), oxygen saturation (SaO_2), peak inspiratory pressure (PIP), and temperature (T). The examiner recorded the recalled values as well as the actual current monitor values of these parameters. We compared recalled and actual parameter values to determine if the recalled values were within clinically relevant error limits[3]. Due to technical difficulties, we only interviewed eight anesthetists in each record keeping category. The video-tapes were reviewed and the anesthetist's intraoperative time was categorized into 15 predefined activities (figure insert).

There was no significant difference between the percent case time spent recording manually (12.7%, ±4.4%) and automatically (14.6%, ±2.7%) (figure). The anesthetist was somewhat less aware of the patient's vital signs when charting manually (figure insert).

Record keeping time is not reduced with the AARK; it is reallocated from manual charting to the anesthetist-machine interface. Vigilance is not adversely affected by the AARK.

References
1. J Clin Monit 1989;5:270-283
2. Safety and Cost Containment in Anesthesia 1988, pp 224-5
3. Anesthesiology 1990;73 (supplement):A416



S80

Title: THE EFFECT OF HYDROSTATIC PRESSURE ON HALOTHANE BINDING IN RAT BRAIN SYNAPTOSOMES

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Pressure reversal of anesthesia has been observed in intact organisms at pressures of from 50 to 100 atmospheres (ATM)(1). This phenomena has been attributed to either a physical displacement of anesthetic molecules from their site of action due to volume compression, or to influences on a separate site which then functionally competes with effects produced by the anesthetic. This latter possibility does not rely on removal of the anesthetic from its site of action. We have recently shown that halothane binds in a saturable and specific manner to rat brain synaptic membranes using photoaffinity labelling techniques (2), and have now extended these observations to address the question of whether halothane binding is altered at pressures which produce reversal of anesthesia in intact organisms. Synaptosomes were prepared by conventional methods. Samples for photolysis (1 mM Na_2HPO_4, 0.32 M sucrose buffer containing 10 mM glutathione, 0.1 mM ^{14}C-halothane (0.83 mCi/mmol) and 1.2 mg synaptosomal protein) were exposed for 5 minutes to the focused UV output of a 200 W Hg lamp after reflection from a dichroic mirror with constant stirring in a 3.5 ml chamber with a 2 cm quartz window. Hydrostatic pressure of 0, 1000 or 2000 psi was achieved with no change in temperature (15°C) or gas tension using a hydraulic hand pump. After exposure and decompression, the samples were filtered, and washed with 2°C buffer, and the radioactivity retained on the GF-B filters was determined via liquid scintillation. Total synaptosomal labelling was (in DPM/mg protein) 15092±1855 for 0 psig, 16233±1472 for 1000 psig and 18272±750 for 2000 psi (n=3 each, F=2.42, P=NS). Similar results were obtained in another tissue: liver mitochondria, (DPM/mg protein) 3701±352 for 0 psig and 3449±211 (n=3 each, P=NS). These data are not consistent with a physical displacement of halothane molecules as being responsible for the pressure reversal of this anesthetic agent in the rat, and suggest that pressure and anesthesia act at distinct sites.

Refs:

(1) Wann KT and MacDonald AG. Actions and interactions of high pressure and general anesthetics. Prog. Neurobiology. 1988 30: 271-307
(2) El.Maghrabi EA, Eckenhoff RG, Shuman H. Saturable binding of halothane to synaptosomal membranes of rat brain. Anesthesiology 1991; (abstract in press).

S81

Title: CEREBRAL BLOOD FLOW VELOCITY PATTERNS DURING LOW-FLOW CARDIOPULMONARY BYPASS: ? HYSTERESIS BEHAVIOR

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INTRODUCTION: Cerebral blood flow velocity (CBFV) patterns during low-flow cardiopulmonary bypass (CPB) have not been described. Greeley(1) has shown that after low-flow CPB cerebral blood flow returns to initial values(2) Other work suggests that a higher cerebral perfusion pressure (CPP) is necessary after low-flow CPB to produce a CBFV equal to pre low-flow values. These apparently contradictory conclusions can be reconciled if hysteresis behavior exists in the resistance vessels of the cerebral vasculature. The purpose of this study was to investigate CBFV patterns during low flow CPB.

METHODS: With institutional approval we studied 4 patients < 1 year of age undergoing corrective cardiac surgery and requiring low-flow CPB. Anesthesia consisted of fentanyl 50-100 µg/kg and pancuronium. Ventilation was with air/oxygen ($PaCO_2$ 35-40mmHg). No cerebral vasoactive agents were used. Intracranial pressure (ICP) was estimated from anterior fontanel pressure. Mean arterial blood pressure (MAP) was measured using an indwelling arterial catheter. CBFV was monitored in the middle cerebral artery using a Transpect TransCranial Doppler (TCD). Patients were established on CPB and cooled to a nasopharyngeal temperature (NPT) between 17.5-28.8°C (α-stat). CPB pump flow (Q) was decreased in 50cc/min decrements until cerebral perfusion disappeared. Q was increased back to initial flow values. MAP, ICP and CBFV were continuously recorded. CPP was calculated as MAP-ICP. Data are expressed as mean(±SD). At a chosen CPP of 20 mmHg, a Student-t-test was performed between decreasing and increasing CBFV. $P<0.05$ was accepted.

RESULTS: Mean (±SD) age, weight and NPT were 24±22wks, 4.6±1.4 kg and 25±5.2°C respectively. As Q decreased MAP, CPP and CBFV decreased. During increasing CPP the CBFV was greater at any given CPP than during decreasing CPP ($p<0.05$)(fig.1). This pattern was reproduced in all patients.

DISCUSSION: The pattern of CBFV during increasing CPP is different from that during decreasing CPP (Fig.1). This may be explained by hysteresis behavior in the resistance vessels. The transmural pressures during decreasing CPP are less than during increasing CPP.(3) This suggests that resistance vessels at the same CPP, during the period of decreasing CPP, are larger than during the period of increasing CPP. This would account for both the higher CPP necessary to reestablish detectable CBFV and the greater CBFV during increasing CPP.

REFERENCES: Circulation 1989;80:I-209 2)J.Cardiovasc Tech 1991;9:250 3)Am J. Physiol. 1955;180:83

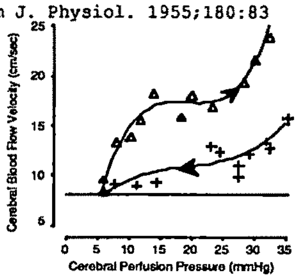

Fig 1. CBFV during decreasing and increasing CPP.

S82

Efficacy of EMLA (Eutectic Mixture of Local Anesthetic) cream for venipuncture in children

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BACKROUND AND RATIONALE Venipuncture may be the most upsetting aspect of a child's OR visit. To attenuate the pain of venipuncture, a topical cream-EMLA is currently under investigation in children. EMLA is a mixture of 2.5 grams of lidocaine plus 2.5 grams of prilocaine per 100 grams of cream and can be applied to the dorsum of the hand to provide local anesthesia for venipuncture. In this study we undertook to determine the utility of EMLA cream for venipuncture in children.

EXPERIMENTAL PROTOCOL With approval of the hospital ethics committee informed parental consent was obtained for a randomized double blind study of 60 ASA I and II patients, unpremedicated, 5-12 years of age scheduled for ambulatory surgery. Patients with allergy to prilocaine or lidocaine were excluded. Children were assigned to one of two groups; placebo or EMLA. Two and a half grams of cream which contained either placebo or EMLA was applied to the dorsum of the hand and covered with a Tegaderm®. The patients were then instructed regarding the pain rating scale. After 60 minutes, venous cannulation was performed by one of the authors using a 24 gauge angiocath. Blood pressure heart rate and respiratory rate were measured before and immediately after cannulation of the vein. Pain was assessed via 2 methods by patients; visual analogue scales (VAS) and a verbal assessment. Anesthesiologists rated pain via VAS and patient cooperation scale rating. Data were compared ($p<0.05$) using the Mann Whitney U-test.

RESULTS Initial analysis of the data revealed blood pressure, heart rate, respiratory rate before and immediately after venous cannulation did not differ significantly between groups. Age, weight, application time, redness, pallor and edema at the site of application, showed no significant difference between the 2 groups. Neither verbal assessment and VAS by patient nor cooperation scale rating and VAS by investigator showed any significant difference between the two groups.The data was complex and will require further analysis.

DISCUSSION Pain free venous cannulation depends on the elimination of both the anticipation of a painful stimulus and the actual pain of skin puncture. Although previous studies have demonstrated the effectiveness of EMLA's analgesic properties[1,2,3], its ineffectiveness in this study may be attributed to 1)inconsistency between pain rating methods 2)those expert at inserting iv's in awake children may not be aided by EMLA and 3)pain from needle puncture may be less distressing than it's anticipation. EMLA alone should have no effect on the anticipation of pain. In patients who have received sedative premedication the analgesic properties of EMLA may provide an ameliorating effect.

REFERENCES

1)Anesthesiology 1988;68:804
2)Br.J.Anaesth.1986;58:1242
3)Anesthesiology 1982;57:340

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S83

TITLE: **POSTANESTHETIC HYPOXEMIA DETECTED BY CONTINUOUS TELEMETRIC PULSE OXIMETRY**

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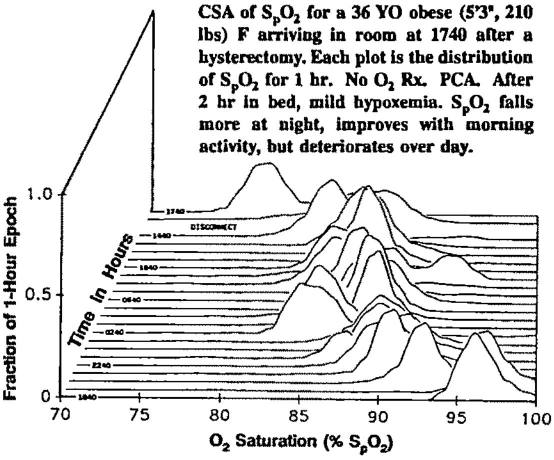
Routine in-patients are abruptly much less closely monitored and attended after leaving the monitor-intense PACU. Telemetric artifact-free measurement of oxygen saturation was used in this study to monitor continuously S_pO_2 during the 24 hours following PACU discharge.

METHODS: With Committee on Clinical Investigations approval, 93 GA pts randomly selected by hospital room gave informed consent to be monitored immediately upon arrival from PACU with an ECG-synched pulse oximeter (Nellcor N-200) connected to a Nellcor "Oxinet" computerized telemetric pulse oximetry network (TPON) which records HR, plethysmographic amplitude, and S_pO_2 every 10 s. No data were visible to anyone during collection. Vital signs, oxygen therapy (O_2 Rx), pain medication, and events were manually recorded. TPON data were passed through a separate previously validated signal-processing algorithm[1] that rejects disconnects and artifacts before displaying S_pO_2. Hypoxemia was defined as: mild: 95-90%; moderate: 89-85%; severe: $\leq$ 84% ($<P_aO_2 = 54$ mm Hg). Comparisons were by Fisher's exact and t tests and ANOVA.

RESULTS: The TPON monitoring was well tolerated. Age 19-90, the pts' surgery included: 38 pelvic, 22 abdominal, 1 thoracic, 32 other. Disconnects excluded, mean TPON time = 17.5 hours, 4.3% = signal artifact (0.4-25.8%). 50 pts had a progressive change in S_pO_2: 44 down and only 6 up. In the population, mean hypoxemic time = mild-22.1%, moderate-2.9%, severe-0.6%. Hypoxemia >5% of time: 72 pts mild, 12 moderate, 3 severe. Considering factors in relation to hypoxemia: no correlations with age or pelvic surgery; lack of O_2 Rx correlated with mild hypoxemia ($p<.01$); obesity strongly correlated with moderate ($p=.0003$) and severe ($p<.0001$) hypoxemia; and PCA possibly correlated ($p=.057$) with severe hypoxemia. By ANOVA, O_2 Rx strongly interacted with obesity to affect the S_pO_2 in both moderate ($p=.016$) and severe ($p=.006$) hypoxemia. There were no adverse patient events due to hypoxemia recorded during the monitoring.

DISCUSSION: This accurate, continuous, long-term, automated TPON of postanesthetic (or any) pts is feasible, is a valuable safety monitor for selected pts at risk for hypoxemia, and dramatically improves upon manual S_pO_2 notations with subjective artifact evaluation. Although no accidents occurred, many dramatic desaturations neither suspected or detected at the time of their occurrence were captured. The data show postanesthetic obese patients benefit from continuous O_2 Rx. Additional evaluation of pain therapies and other factors possibly contributing to hypoxemia on the patient-care hospital floor as well as of patient outcome is warranted.

[1] Pan PH, James CF. Anesthesiology 73:A543 and A943, 1990



CSA of S_pO_2 for a 36 YO obese (5'3", 210 lbs) F arriving in room at 1740 after a hysterectomy. Each plot is the distribution of S_pO_2 for 1 hr. No O_2 Rx. PCA. After 2 hr in bed, mild hypoxemia. S_pO_2 falls more at night, improves with morning activity, but deteriorates over day.

S84

Title: SAFETY AND EFFICACY OF DESFLURANE IN PERIPHERAL VASCULAR SURGERY

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Introduction The purpose of this study was to compare the safety and efficacy of desflurane D, a new potent inhaled anesthetic with that of isoflurane (I) in patients with peripheral vascular disease scheduled for revascularization of a lower extremity.

Methods Following IRB approval and written informed consent we studied 46 patients, ASA PS 2 or 3 scheduled for femoro-popliteal bypass surgery. Each was randomly assigned to receive either D or I. Patients were premedicated with diazepam 5-10 mg p.o. Anesthesia was induced with fentanyl and thiamylal or thiopental, and relaxation with succinylcholine. During induction patients received 1-3 MAC of D or I. Following tracheal intubation anesthesia was maintained with D or I in N_2O (50-60%) and oxygen. Relaxation was maintained with vecuronium. Blood pressure, heart rate, SpO_2, ECG, and end-tidal D or I concentrations were recorded. Following discontinuation of the inhaled agent, times to eye opening, squeezing of hand, giving name and date of birth were noted. Data were analyzed using a two-tailed Student's t test (unpaired) and comparison of proportions. Data are expressed as mean ± S.D. P<0.05 was considered significant.

Results - See Table

Discussion D was as safe and efficacious as I in this study population. Recovery from D was more rapid than following I. There was a non-significant increase in postoperative analgesia (morphine) requirement in the PACU following D.

	Desflurane (D)	**Isoflurane (I)**
n	24	22
M/F	17/7	12/10
Age (yrs)	63±11	64±11
Durn.Surgery (min)	236±73	239±111
Avg. ET agent (MAC)	0.48±0.22	0.38±0.16
Tot. Fentanyl (mcg)	227±116	266±203
ET MAC at case end	0.3±0.2	0.3±0.2
Peak ET (MAC)	1.4±0.7	1.1±0.6
Time to:		
Eye opening (min)	5.8±3.7*	10.6±7.5*
Squeeze fingers (min)	7.9±4.7*	14.6±14.6*
Date of birth (min)	12.3±8.8*	22.6±20.1*
Giving Name	12.0±8.51	9.5±18.5
ECG changes in PACU	11	11
Hemat/Chem Labs	No changes	No changes
Intraop need for vasopressor/depressor	15	17
Need for morphine analgesia in PACU	15/24	8/22
Nausea/Vomiting PACU	3	1

* p < 0.05 between groups

S85

TITLE: TOPICAL CLONIDINE FAILS TO REDUCE POSTOPERATIVE STRESS RESPONSE AFTER NONCARDIAC SURGERY

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AFFILIATION: Departments of Anesthesia and Critical Care and Medicine, The University of Chicago, Chicago, IL 60637

INTRODUCTION: Previous work suggests that regional[1] and sufentanil[2] anesthetics suppress the stress response after noncardiac surgery (NCS), improving patient outcome. We hypothesized that clonidine (CL), delivered throughout the perioperative period by simple topical application, would also effectively block the postoperative stress response. We performed a double-blinded, randomized, placebo-control study to test this hypothesis.

METHODS: After IRB and patient approval, 25 patients undergoing NCS were randomly allocated. The CL group received a CL skin patch (0.2 mg/day) the night before surgery and CL 0.3 mg oral loading dose 60-90 min before surgery. The control group received placebo patches and pills. General anesthesia was induced with sufentanil 0.5 mcg/kg, thiamylal up to 5 mg/kg; maintenance was with 50% N_2O, vecuronium, enflurane (maximum 2% inspired), and any additional sufentanil needed to control hemodynamics within 20% of ward baseline. All patients were extubated in the OR. Analgesia was provided with IV morphine. On the first postoperative day (POD 1) between 7 and 9 AM, samples were drawn for serum cortisol and plasma norepinephrine (NE). Serum cortisol was determined by an immunoassay in 21 patients. Plasma NE was determined in patients by HPLC by averaging 3 different samples drawn at 30 min intervals. Serum glucose values on POD 1 were compared to results drawn the day before surgery. Unpaired 2-sample T tests were used to analyze data.

RESULTS: Results are summarized in the table below. There were 12 patients in the CL group (NE determined in 10) and 13 in the control group (NE determined in 11). Neither cortisol levels ($p > .20$) nor NE ($p > .24$) levels were different between the two groups. There was no difference in the rise in serum glucose between the two groups ($p > .59$).

DISCUSSION: Our results show that topical CL does not reduce the stress response (NE glucose, or cortisol levels) measured on POD1. Previous studies have demonstrated that oral CL reduces levels of NE intra- and immediately post-operatively.[3] Higher doses of CL may be needed to decrease POD1 stress response. Alternatively, further work in larger groups of patients may show statistically significant differences. Further work is necessary to test these hypotheses.

REFERENCES: 1.Anesthesiology 66:729-736,1987. 2.Anesthesiology 65:A516,1986. 3.Anesthesiology 67:11-19,1987

Supported by a grant from FAER.

	CONTROL	CLONIDINE
Patients (n)	13	12
Age (yrs)	67.6 ±2.2 (SEM)	68.6 ±3.5 (SEM)
NE POD1 (pg/ml)	855 ±192 (SEM)	587 ±252 (SEM)
CortisolPOD1 (mcg/dl)	21.3 ±2.8 (SEM)	16.5 ±2.2 (SEM)
Rise in glucose (mg/dl)	34.4 ±10.3(SEM)	15.1 ±32.7 (SEM)

S86

TITLE: CLONIDINE (ORAL AND TOPICAL) DECREASES HEART RATE IN THE FIRST 20 POSTOPERATIVE HOURS

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INTRODUCTION: Postoperative myocardial ischemia (PMI) predicts postoperative cardiac complications and is associated with tachycardia;[1] therapy which reduces heart rate (HR) after surgery may be beneficial. Clonidine (CL) given IV, lowers HR during the first 5 hours after aortic surgery.[2] We hypothesized that HR could be lowered in a sustained fashion using topical CL in the first 24 hours after surgery. We performed a double-blinded, randomized, placebo-control study to test this hypothesis.

METHODS: After IRB and patient approval, 25 high-risk patients undergoing major noncardiac surgery (NCS) were randomly allocated. The CL group received a CL skin patch (0.2 mg/day) the night before surgery and CL 0.3 mg oral loading dose 60-90 min before surgery. The control group received placebo patches and pills. General anesthesia was induced with sufentanil 0.5 mcg/kg, thiamylal up to 5 mg/kg; maintenance was with 50% N_2O, vecuronium, enflurane (maximum 2% inspired), and any additional sufentanil needed to control hemodynamics within 20% of ward baseline. All patients were extubated in the OR. Analgesia was provided with IV morphine. HR was measured hourly in an ICU setting.

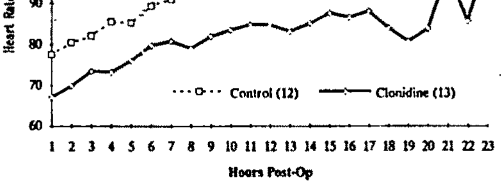
Eighteen patients were monitored during surgery and for at least 10 hours postoperatively with a semi-continuous 12 lead ST segment monitor (ELI100, Mortara Instruments) with frequency limits of 0.05 Hz to 160 Hz. EKGs were read by a cardiologist unaware of the clinical scenarios. EKGs were considered ischemic if there was more than 1 mm downsloping ST segment depression in any lead compared to the preoperative baseline. Unpaired two-sample T tests and chi-square analysis were performed.

RESULTS: Results are summarized in figure 1. Patients in the CL group had significantly lower HR ($p<0.05$) at 1, 4, 5, 8, 14, 19, and 20 hours after surgery (see Fig 1). However, there was no change in the rate of PMI (3/10 CL group vs 3/8 placebo).

DISCUSSION: We have shown that the use of a CL skin patch (after an oral loading dose) reduces postoperative HR in NCS patients. Further work in larger numbers of patients is necessary to substantiate if reduction in HR in the first 24 hours after NCS by topical CL this simple regimen is associated with a reduction in the incidence of myocardial ischemia and its complications.

REFERENCES: 1.Am J Card 64:1113, 1989 2.Anesthesiology 71:A155,1989. 3.NEJM 323:1781-8,1990.

Supported by a grant from FAER.



S87

TITLE: The Influence of Propofol with and without Nitrous Oxide on Cerebral Blood Flow Velocity and CO_2 Reactivity in Man

AUTHORS: C. Eng M.D., A. Lam M.D., T. Mayberg M.D., T. Mathison R.N., C. Lee M.D.
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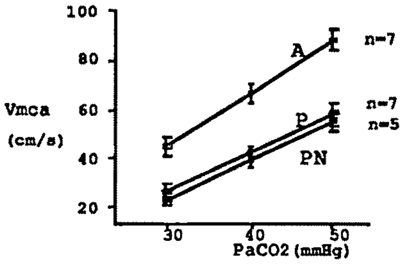
Univ. of Washington, Seattle, WA

Introduction: Hypocapnia is frequently used in neuroanesthesia to decrease cerebral blood flow (CBF) and intracranial pressure (ICP). In limited studies,[1,2] propofol has been shown to cause cerebral vasoconstriction and to preserve CO_2 reactivity. In the present study we evaluated the cerebral vascular effect of propofol with and without N_2O during varying levels of P_aCO_2 using the noninvasive technique of transcranial Doppler ultrasonography (TCD).

Method: After institutional approval, 7 consenting adults (age 24-36 yrs) without systemic diseases undergoing non-neurological surgery were studied. Using a Transpect (Medasonics) monitor with the angle of insonation fixed by a head harness throughout the study, the middle cerebral artery flow velocity (V_{mca}) during varying levels of P_aCO_2 (25-55mmHg) was measured under the following conditions: **(A)** awake baseline, **(P)** propofol 2.5mg/kg bolus followed by continuous infusion of 150ug/kg/min while being ventilated with100% O_2, and **(PN)** propofol as in the condition above + 70% N_2O/30% O_2. Neuromuscular blockade was maintained with vecuronium. While awake, hypocapnia was induced by voluntary hyperventilation and hypercapnia was induced with rebreathing 10% CO_2 in a closed circuit. While anesthetized hypocapnia and hypercapnia were induced by manipulation of minute ventilation. A minimum of 5-6 simultaneous measurement of V_{mca} and P_aCO_2 data points were obtained under each study condition. Systemic blood pressure was monitored via a radial arterial catheter and phenylephrine administered if MAP was < 60mmHg (phenylephrine was used in 3 of 5 patients in the PN group). Linear regression analysis was used to calculate the slope of CO_2 reactivity in each patient under all study conditions. Normalization of data was then achieved by calculating the V_{mca} for P_aCO_2 at 30, 40 and 50 mmHg from the linear regression equation. ANOVA for repeated measures and Fisher's PLSD were used for comparison between the study conditions.

Results and Discussion: At all levels of P_aCO_2 in **(P)** and **(N)**,V_{mca} was significantly lower when compared with **(A)**. Compared to the CO_2 reactivity slope during **A** of 2.1±0.3 $cm.s^{-1}.mmHg^{-1}$, the slopes of **(P)** and **(PN)** were significantly reduced by 27% and 24% respectively, $p<0.05$ (see graph). Considering that V_{mca} was reduced at all CO_2 levels in **(P)** and **(PN)**, the reduction in slope was not unexpected. Indeed, dividing the absolute slope by their respective V_{mca} at 40 mmHg to derive the relative CO_2 reactivity slope yielded no significant difference between the study conditions. We conclude that propofol is an anesthetic agent with vasoconstrictive properties on the cerebral vasculature and that the addition of N_2O does not influence the vasoconstriction nor the CO_2 reactivity. Hypocapnia therefore can be used effectively during propofol anesthesia with or without nitrous oxide in patients with increased ICP .



References: 1. *Anaesthesist* 36:60-65, 1987.
2. *Anesthesiology* 73:404-409, 1990.

S88

TITLE: Pharmacokinetic Parameters From Computer Assisted Continuous Infusion of Vecuronium

AUTHORS: RH Epstein, MD, C Wilkerson, MD, RR Bartkowski, MD, PhD, J Finke, BS, H Schieren, PhD
AFFILIATION: Department of Anesthesiology, Jefferson Medical College, Phila, PA

Introduction Computer assisted continuous infusion (CACI) rapidly achieves a constant blood drug level using an infusion pump whose rate is adjusted according to a pharmacokinetic model. When applied to neuromuscular drugs, this approach should lead to a constant level of blockade. Accurate determination of central compartment volume and related rate constants are important for devising CACI programs. These parameters may not be accurately determined when a bolus of drug is injected. We devised an alternate approach to determine kinetic constants using CACI and non-linear curve fitting.

Methods With Institutional Review Board and patient consent, we studied 5 patients undergoing spinal fusion. Using published 3-compartment kinetic parameters(1) a CACI program for vecuronium was developed. Arterial blood was periodically sampled during a 16 minute CACI, then for 16 minutes following discontinuation of the infusion. Plasma vecuronium was measured by gas liquid chromatography. Using Euler's approximation to the solution of a 3 compartment model(2) k12 and k21, and V1, were optimized by the Simplex method of nonlinear regression,(3) taking as starting values the published rate constants. Because of the short duration of the infusion, we did not optimize k10, k13, or k31 (0.099, 0.086, 0.013, respectively).

Results The published and optimized rate constants are presented in the Table. Actual concentrations from a typical patient, and the kinetic fits using published and optimized rate constants are shown in the Figure.

Discussion Using this approach, we obtained a smaller central compartment volume and larger k12 and k21 rate constants than previously published. We believe these differences are due to underestimation of peak concentration during the conventional approach. Our approach may lead to improved CACI protocols.

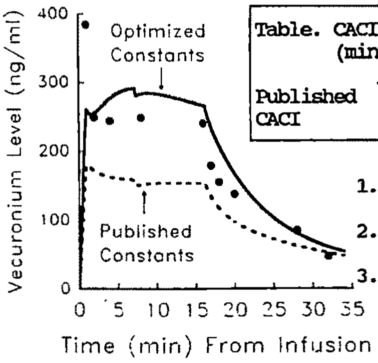


Table. CACI Rate Constants (min^{-1}) and V1 (ml/kg)

	k12	k21	V1
Published	0.230	0.190	48.0
CACI	0.362	0.836	32.3

REFERENCES
1. Anesthesiology 58:405, 1983
2. Anesthesiology 68:261,1988
3. Numerical Recipes: The Art of Scientific Computing. pp 615-688

S89

Title: REPETITIVE ADMINISTRATION OF NEOSTIGMINE MAY CAUSE INCREASED NEUROMUSCULAR BLOCK

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Linkoping University Hospital, Linkoping, Sweden

Introduction:

Repetitive administration of neostigmine has been demonstrated to cause an increased tetanic fade in anesthetized humans in the absence of neuromuscular blocking agents (1,2). Other investigators failed to show an increased neuromuscular block following reversal with neostigmine at routine train-of-four (TOF) stimulus frequency (3). In the clinical situation, repeated doses of neostigmine are most often given at short time intervals. Thus, there is still a controversy regarding the possible transmission failure induced by repeated doses of neostigmine given for reversal of neuromuscular block. The aim of this investigation was to study the effect of repeated doses of neostigmine on the neuromuscular transmission during recovery after vecuronium using TOF nerve stimulation.

Method:

The study was approved by the Ethics Committe of Linkoping University Hospital. Six otherwise healthy patients were included following informed consent. Anesthesia was induced with thiopentone and fentanyl and maintained with 0.5 % isoflurane in nitrous oxide and oxygen (70/30 %). Tracheal intubation was performed after a bolus dose of vecuronium of 0.08 mg/kg i.v. All patients were mechanically normoventilated as monitored with capnography, oximetry and pulse oximetry. Core temperature was normal and peripheral skin temperature was kept >32.0 °C throughout the study. The neuromuscular transmission was evaluated using mechanomyography of the adductor pollicis muscle after supramaximal TOF stimulation (2 Hz for 2 seconds every 12 second) of the ulnar nerve at the wrist using a Myograph 2000 neuromuscular transmission analyser (Biometer, Denmark). When the neuromuscular block had recovered to a TOF ratio of 0.25 neostigmine 40 µg/kg and glycopyrrolate 8 µg/kg was given i.v. At a TOF ratio of 0.90, a second dose of neostigmine 40 µg/kg and glycopyrrolate 8 µg/kg was given i.v. The TOF ratio was then recorded until the TOF response had reached a ratio of 0.90 again.

Results:

Data is given as range (mean ± s.d.)

Recovery time between a TOF ratio of 0.25 and 0.90 was 3.0-8.0 minutes (5.2 ± 1.7). Following the second dose of neostigmine, all patients showed a continuously reduced TOF ratio. The minimum TOF ratio recorded was 0.69-0.89 (0.82 ± 0.07) which was reached after 2.0-4.0 minutes (3.2 ± 0.7). The time until a TOF ratio of 0.90 was reached again was 6.0-16.0 minutes (10.9 ± 4.4). Thereafter a complete TOF recovery was achieved in all patients within 10 minutes.

Discussion:

The major finding was that repetitive administration of neostigmine in clinical doses caused an increased TOF fade during reversal of vecuronium. These findings was obtained when the two doses were repeated within a short time interval, i.e. 3.0 to 8.0 minutes in normothermic patients during a standardized anesthetic procedure. In accordance with initial reports (1), neostigmine-induced transmission failure was demonstrated by increased fade during TOF stimulation. It is possible that the observed neostigmine effect may originate from a presynaptic interaction with acetylcholine release or by channel block (4). Our data suggests that reversal of neuromuscular block by repetitive administration of neostigmine 40 µg/kg within short time interval, may cause a failure of neuromuscular transmission.

References:

1. Br J Anaesth 52:69-76,1980
2. Br J Anaesth 59:983-988, 1987
3. Anesthesiology 71:A798, 1989
4. Eur J Anaesth 2:59-93, 1985

S90

Title: DEXTRAN ENHANCES THE EFFECT OF PLASMINOGEN DURING SURGERY

Authors: M. Eriksson M.D., Ph.D. &
T. Saldeen M.D., Ph.D.

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Introduction: Dextran increases plasminogen activation rate *in vitro* (1,2). Since this compound is commonly used during surgery as a blood substitute we decided to explore whether such an effect occurs in man.

Methods: Thirty-one patients (ASA: I-II; Mean age: 63 years) undergoing laparotomy were given a total amount of 500 ml dextran 70. Nine patients serving as controls were merely given a glucose-electrolyte solution. Blood samples were analyzed for tissue plasminogen activator inhibitor activity (PAI:act), tissue plasminogen activator activity (t-PA:act) and tissue plasminogen activator antigen (t-PA:ag). Corrections for haemodilutions were done. $p < 0.05$ was considered significant. Multiple regression analysis of the material was performed.

Results: PAI:act decreased 19% after 250 ml of dextran; after 500 ml the activity was decreased by 22% as compared to levels prior to the infusion. The activity of t-PA increased 43% and 29%, respectively. The concentration of t-PA:ag increased 18% and 15%, respectively. All differences were significant. No changes were seen among the control patients. Correlations between changes in PAI:act; t-PA:act and t-PA:ag were calculated. The strongest correlation, was an inverted relation between PAI:act and t-PA:act (r= -0.51 ; P= 0.96) followed by a connection between the elevations of t-PA:act and t-PA:ag (r= 0.45 ; P= 0.93).

Discussion: We have demonstrated that dextran may improve fibrinolytical parameters during surgery. This effect seem mainly to be due to an increase in t-PA:act and, subsequently, a decrease in PAI:act. The effect on t-PA:act may be explained by the ability of dextran to increase enzymatic activity (3).

The close correlation between the increase in t-PA:act and t-PA:ag makes it impossible to exclude the possibility that dextran may release t-PA, primarly, from the vascular endothelium.

References: 1. Thrombosis Res. 19:103, 1980.
2. Thrombosis Res. 19:535, 1980.
3. Biochem. J. 89:253, 1963.

S91

TITLE: HALOTHANE-INDUCED VASODILATION OF CANINE CEREBRAL ARTERIES MAY BE MEDIATED THROUGH CYCLIC GMP FORMATION

AUTHORS: Hanna Eskinder Ph. D., Cecilia J Hillard Ph.D. Noel Flynn, M.B., Zeljko J. Bosnjak, Ph. D., John P. Kampine, M.D., Ph.D.,
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Although halothane is a potent vasodilator, the biochemical mechanisms by which halothane induces vasodilation are not well known. Sprague et al (Anesthesiology 1974,40:162) found halothane and isoflurane to increase intracellular cAMP in rat aortic smooth muscle. However, the direct effect of volatile anesthetics on cyclic guanosine 3,5-monophosphate (cGMP) levels and guanylate cyclase enzyme activity in vascular smooth muscle have not been reported. The purpose of the present study was to examine the effects of halothane on the guanylate cyclase-cGMP system in canine middle cerebral arteries.

Rings of cerebral arteries preconstricted with 5-hydroxytryptamine (0.2 μM) were exposed for 15 min to low (0.59 mM, equivalent to 1.8 %) or high (0.9 mM, equivalent to 2.9 %) concentrations of halothane or for 5 min to sodium nitroprusside (SNP, 50 μM). The vessels were instantaneously frozen by immersing them in liquid nitrogen, homogenized and the tissue cGMP levels were determined using radioimmunoassay. Halothane produced 2.23 ± 0.44 and 4.47± 0.87 fold increase in tissue cGMP levels over control at 1.8 and 2.9 %, respectively. SNP, a nitrovasodilator, also increased the tissue cGMP level to 7.80 ± 1.36 fold of the control value.

To better understand the mechanisms of halothane-induced increase of tissue cGMP level, the effects of this anesthetic agent on guanylate cyclase enzyme activity were examined. Guanylate cyclase, an enzyme which catalyzes the formation of cGMP from GTP, exists in both the soluble and particulate (membrane) fractions of vascular smooth muscle cells. In the present study cerebral arteries were homogenized in cold 0.25 M sucrose / 5 mM Tris-HCl (pH=7.4). A crude soluble extract was obtained by centrifugation at 37,000 x g for 60 min at 4°C. The supernatant was recovered and used in the soluble guanylate cyclase assay. The pellet was resuspended in the homogenization buffer and used in the particulate guanylate cyclase assay. The enzyme activities were quantified by measuring cGMP levels in the presence of 2.5 mM IBMX and 10 mM theophylline, phosphodiesterase inhibitors. SNP, but not halothane, stimulated the activity of the soluble guanylate cyclase. However, halothane like Atrial natriuretic factor (ANF, 50 μM) stimulated the particulate guanylate cyclase activity. (See Table below)

cGMP	Basal	HAL(1mM)	SNP(50μM)	ANF(50μM)
Soluble Fraction (nmole/100mg protein)	1.5±0.3	1.3±0.2	30.8±4.4	
Particulate (nmole/mg protein)	1.6±4	4.8±1.4		6.4±2.03

These results suggest that halothane-induced vasodilation of cerebral blood vessels is partly mediated through a rise in tissue cGMP level. The increase in cGMP level induced by halothane results, at least in part, from activation of the particulate but not the soluble guanylate cyclase enzyme. The present study, however, does not rule out the possible interaction of halothane with the cGMP phosphodiesterase enzymes.

S92

Title: POWER SPECTRUM OF HEART RATE VARIABILITY AS A PREDICTOR OF BRADYCARDIA FOLLOWING INDUCTION OF SUFENTANIL ANESTHESIA

Authors: F. Estafanous MD, J. Brum MD, M. Ribeiro MD, M. Estafanous BS, N. Husni BS, N. Starr MD.
Affiliation: Division of Anesthesia, Cleveland Clinic Foundation, Cleveland OH

Introduction: Hemodynamic and heart rhythm changes during induction of anesthesia may affect myocardial perfusion and cause ischemia in patients with coronary artery disease(1). Analysis of power spectrum of the heart rate (PSHR) variability can supply information on the autonomic nervous system that may be involved in this phenomenon (2,3).

Method: In this study, we evaluated 78 patients undergoing coronary bypass graft surgery. Before and after induction of anesthesia the heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), cardiac index (CI) and PSHR components were recorded. Decreases in HR greater than 20% following induction with sufentanil and vecuronium defined two groups of patients: bradycardic (B) and not bradycardic (NB). PSHR was obtained by using a special algorithm and data acquisition system for real time spectral analysis. A low frequency component (LFa, mainly sympathetic) was analyzed from a band of 0.04 Hz to 0.1 Hz. A high frequency component (RFa, parasympathetic) was identified by the respiratory frequency spectrum. The variables were analyzed and compared between B (n=25) and NB (n=53) groups in order to verify the possibility of identification of patients prone to hemodynamic alterations after anesthesia induction.

Results: There were no differences in HR, MAP, CO or CI between groups before anesthesia induction. However, the PSHR analysis showed significant differences between LFa/RFa ratio of the NB (4.38±0.63) and B (7.30±1.31) [Fig 1] and RFa of the NB (1.04±0.22 bpm²) and B (0.34±0.08 bpm²) groups before induction of anesthesia. [Fig 2].

Discussion: Our data showed that patients which developed bradycardia had lower parasympathetic activity than patients that maintained stable HR following anesthesia induction. This investigation suggests that PSHR may identify patients of high risk for developing hemodynamic changes following anesthesia.

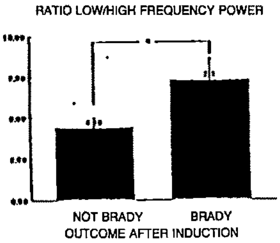

Fig 1

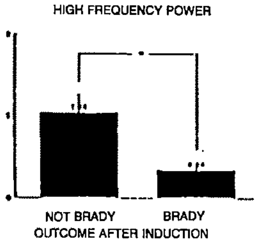

Fig 2

References: (1) *Anesthesiology* 1986;64,4:521-523, April. (2) *Science* 1981;213:220-222.(3) *Am J Physiol 1985*;248:H151-H153.

S93

Title :**EFFICIENCY AND IMPORTANCE OF AIRWAY FILTERS IN REDUCING MICRO-ORGANISMS**

Authors :J.M.Fargnoli M.D.,C.C. Arvieux M.D., F.Coppo M.D., P.Girardet M.D. and J.H.Eisele Jr.M.D.*
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Introduction: Anesthesia litterature and practice has paid little attention to the benefits of filtering the breathing system which can protect against contamination of equipment, patients, and environment. Current filters used mainly for heat conservation range widely in filtering effectiveness, hence we chose to study three (A,B, and C) devices used in Europe for their ability to remove both bacterial and viral micro-organisms.

Methods: Pseudomonas diminuata (0.3 to 0.8 microns) and Bacteriophage MS-2, a polyhedral virus, (ave. 0.02 microns) were obtained from Industrial and Marine Bacteria Ltd, Scotland. These organisms were prepared in buffered suspensions and analyzed in duplicate using the agar overlay method both before and after presentation to the filters. A sterile nebulizer (De Vilbliss 40) was used with a 28 L/min flow of sterile dry air (1). The efficiency of the nebulizer was determined as: % Efficiency = number of organisms nebulized x 100/ (conc. of organisms entered in the nebulizer) x (vol. nebulized).Each filter was tested 10 times with Pseudomonas and 5 times with Bacteriophage nebulized over 5 min. applications. For each test the affluent total = (vol. x conc.nebulized) x (%Efficiency). Then, the titre reduction (T_R) of the filters was calculated:

$$T_R = \frac{\text{affluent total (no. organisms applied to filter)}}{\text{no. organisms recovered downstream}}$$

The devices were :Filter A:BB22-15 made by Pall Biomedical Products Corporation 77 Crescent Beach Road Glen Cove New-York 11542 U.S.A.Filter B:Humid-Vent Filter made by Gibeck Respiration AB, S-19427 Upplands Väsby, Sweden.Filter C : Hygrobac DAR 352/5411 made by Darex S.P.A. 41037 Mirandola Italy

Results: The effectiveness of blocking bacterial and viral organisms, and reduction in titres by the three filters is shown in th table below:

FILTER	A	B	C
Efficiency of inhibition - %			
Pseudomonas (n=10)	99.9997	99.9485	86.1877
Bacteriophage (n=5)	99.9985	99.0949	96.0022
Reduction in titre - T_R			
Pseudomonas (n=10)	3.42 x 105	1.94 x 103	7.25
Bacteriophage (n=5)	6.96 x 10^4	1.10 x 10^2	25

These data indicate that only 3 out of 1 million bacteria like Pseudomonas pass through filter A, which is significantly better than filter B ($p<0.01$) and C ($p<0.01$) in both efficiency and titre reduction. The differences between filters B and C were not significant

Discussion. Apparently viruses like MS2 (<0.1 micron) develop Brownian motion (2) that increases capture by the filter medium which is hydrophobic and inhibits passage of liquid secretions. Such a mechanism may be important in removing Hepatitis B and other viruses with similar physical characteristics. Other reports show filter A is more effective at lower flow rates (91/min) for at least 75 min (3).

References 1)Duberstein R, Howard g. Sterile filtration of gases ; a bacterial aerosol challenge test . Journal of the Parenteral Drug Associtation 1978,32:192-198
2)Stenhouse J.I.T. Mechanisms of gas filtration, chapter 7,p. 70-76 in Process Engineering Technique Evaluation . Filtration H.K. Suttle ed Morgan-Grampian 1969
3)Latham M.J., Bacterial removal efficiency of the Pall Ultipor breathing system filter BM 2044 1981 Pall biomed. Lmtd Portsmouth England

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S94

Title: ANESTHESIA AFTER HEART TRANSPLANTATION

Author: L.L. Firestone, M.D.
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Introduction: During the 1980s, cardiac transplantation (CTx) became a widely accepted and successful treatment modality for end-stage heart disease. The most common operation, midatrial excision orthotopic procedure, produces complete, permanent vagal and sympathetic efferent denervation (1,2,3). Consequently, there are increasing numbers of survivors with "denervation physiology" who have a high incidence of subsequent general surgery (4). Thus, we investigated the safety of subsequent anesthesia in these denervated patients.

Methods: With institutional approval, anesthesia charts of all procedures performed on 170 consecutive CTx patients between 1/82 and 12/85 were examined. Demographics, subsequent surgeries, anesthetics and adjuvants, and monitoring regimes were compared.

Results: Of the original 170 CTx patients (124 male, 46 female; mean ages 45 ± 11 yrs, 39 ± 10 yrs); 68 underwent a subsequent procedure. Thirty-two underwent anesthesia more than once, for a total of 127 administrations. Forty-five procedures (35%) were emergencies. Thirty-three (26%) were general surgical; 7 (6%) were orthopedic; 6 (5%) were urologic; 5 (4%) were performed on the oral surgery service; there were a few from each of the vascular surgery, opthamology, ENT and neurosurgery services (7% combined). Thirty-eight (30%) occurred within the first month following CTx (13 within 48-hours); 65 (51%) within 6 months. General anesthesia was employed in 61% of cases (78/127); regional in 9% (12/127). Spinal anesthesia comprised the majority of regionals (8/9). PA catheters were employed in 27% of cases (34/127), with insertion almost always immediately prior to, or following, induction. Vasoactive infusions were used in 28% (40/127) of cases, although almost always for brief (< 15 min) durations.

Discussion: Complete cardiac denervation results from division of the cardiac plexus during orthotopic CTx. Such patients may be at risk because the extrinsic mechanisms for responding to new demands are altered (5). Moreover, accelerated atherosclerosis occurs in most donor hearts (6), almost always producing silent ischemia because of afferent denervation. Recipients may also experience rejection, marked by low cardiac output and arrythmias. Although use of PA catheters was common in our series, only 9% of patients required such monitoring during procedures occurring > 1 mo following CTx. A prospective study is underway to address the relationship between rejection episodes or accelerated coronary disease, and the safety of anesthesia following CTx.

References: 1. Circulation 77:162, 1988; 2. J Heart Transpl 7:448, 1988; 3. N Eng J Med 324:1791, 1991; 4. Surgery 98:739, 1985. 5. Int Anes Clin 27:283, 1989; 6. Circulation 76:827, 1987.

S95

Title: GAS EXCHANGE AND COMPLIANCE FOR 24 HOURS FOLLOWING EN BLOC DOUBLE LUNG TRANSPLANTATION

Authors: L.L. Firestone, M.D., S. Firestone, M.D., and B. Davis, B.S.

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Introduction: En bloc double lung transplantation (DLT) has been used to treat a variety of end stage lung diseases, particularly those due to infectious etiologies, primary pulmonary hypertension, or congenital anomalies destructive to parenchyma. Postimplantation, the combined effects of reperfusion injury and lymphatic disruption promote edema formation (1), accompanied by varying alveolar-arterial (A-a) gradients. However few clinical data are available detailing acute effects on arterial blood gases (ABGs) and lung mechanics (2). To develop treatment strategies and help predict postoperative courses, we studied the early ABG and compliance responses to en bloc DLT in 11 consecutive adult recipients.

Methods: With institutional approval, serial ABGs and mechanical ventilator readings (tidal volume; respiratory rate; peak inspiratory pressure; F_iO_2; positive end expiratory pressure) were recorded in this group, at least every other hour for the first 24 hours following weaning from cardiopulmonary bypass.

Results: The age range of study patients (5 males, 6 females) was 25 - 53 years old, and underlying pathological diagnoses included α_1-antitrypsin deficiency, cystic fibrosis, primary pulmonary hypertension, and idiopathic pulmonary fibrosis. Ten of 11 patients survived the study period. One of the 10 survivors manifested severe defects in oxygenation, as well as abnormal ventilation and compliance. In this survivor, high levels of F_iO_2 and/or PEEP were required to maintain oxygenation beginning soon after CPB, and compliance was diminished for the entire study period. More moderate compliance abnormalities and A-a gradients were noted in 5/11 patients, but these resolved within 24 hours. The balance of the study group had comparatively normal early postoperative respiratory parameters.

Discussion: Our data suggest that more than half of patients respond to en bloc DLT with some degree of early respiratory compromise. Thus far, A-a gradients have not been clearly related to either the duration of donor lung ischemia or other factors (1), therefore, detailed clinical data may be most helpful when predicting the postoperative course of DLT patients.

References: 1. Egan TM, Kaiser LR, Cooper JD. Lung transplantation. Curr Prob Surg 26:673, 1989; 2. Gayes JM, Giron JM, Giron L, Nissen MD, Plut D. Anesthetic considerations for patients undergoing double lung transplant. J Cardiothoracic Anesth 4:486-498, 1990.

S96

TITLE: STAUROSPORINE, A PROTEIN KINASE C INHIBITOR, DECREASES THE GENERAL ANESTHETIC REQUIREMENT IN *RANA PIPIENS* TADPOLES

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INTRODUCTION: Protein kinase C (PKC) is an intracellular enzyme found in highest concentration in the mammalian central nervous sytem. Activation of PKC can modulate neurotransmission, by phosphorylating ion channels, receptors, or other synaptic proteins involved in neurotransmitter release (1). We previously demonstrated that the activity of PKC purified from whole brain homogenates can be significantly inhibited by therapeutic concentrations of volatile general anesthetics (GAs) and ethanol (2), but the relationship of these in vitro observations to GA effects in vivo remains to be established. To determine if general anesthesia could involve PKC inhibition, we tested whether a highly potent, specific inhibitor of PKC, staurosporine (STR) (3) decreased the GA requirement in *Rana pipiens* tadpoles.

METHODS: GA concentration-response assays were performed at 20° C on *Rana pipiens* tadpoles, and the anesthetic endpoint of loss-of-righting reflex was used as previously described (4). Prior to assays, STR-treated groups were presoaked for 90 min in 2.5 μM STR (Sigma) dispersed in 10 mM dimethyl sulfoxide (DMSO). (Previous controls established that 10 mM DMSO was without obtunding potency alone or in combination with other agents.) Median effective anesthetic concentrations (EC50) were derived using Waud's method for quantal responses (5). For each GA, STR-treated and control groups were compared by estimating the variance of the difference in EC50 between groups, then referring the ratio of this difference and its standard error to a standard normal distribution. P-values represented the probability of a difference whose magnitude is at least as large as the actual difference, under the assumption that the true EC50 is the same for the two groups (4).

RESULTS: Anesthetic EC50s for the STR and control groups are compared in Table 1. STR produced highly significant decreases in GA requirement for both agents tested ($P < 0.035$ for halothane; < 0.001 for diethylether).

DISCUSSION: These data establish that STR, a *Streptomyces* alkaloid, enhances GA potency in vivo. Furthermore, since STR is relatively specific (6), and our brief preincubations probably limited STR uptake (7), such data support our hypothesis that PKC inhibition could be involved in general anesthesia.

REFERENCES: 1. Science 233:205, 1986; 2. Anesthesiology 73:A706, 1990; 3. Biochem Biophys Res Comm 135:397, 1986; 4. Anesthesiology 66:55, 1987; 5. J Pharmacol Exp Ther 183:577, 1972; 6. Trends Pharmacol Sci 10:218, 1989; 7. Brit J Pharmacol 96:9, 1989.

TABLE 1.

	CONTROL		+STR		n
	EC50	±SE	EC50	±SE	
Halothane	113 μM	11	77 μM	13	200
Diethylether	12.2 mM	0.6	5.0 mM	1.0	235

n = total number of tadpoles studied

S97

Title: ANESTHESIA EXPERIENCE DURING 38 PEDIATRIC CARDIAC TRANSPLANTATIONS

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Introduction: From 1982-89, 44 cardiac transplants (CTx) were performed at Children's Hospital of Pittsburgh (CHP). Medical and surgical aspects of pediatric CTx have been reviewed (1, 2), but few publications relate to anesthetic management. Thus, we analyzed our anesthetic experience with these patients.

Methods: With institutional approval, all children (< 18 y) who had undergone "first time" CTx from 1982-89 were included in the study. Demographics, diagnoses, NPO status, anesthetic technique and vasopressors were compared.

Results: Thirty-three children underwent a simple CTx; 4 received 2 grafts; while 3 patients had both liver & CTx. Among 37 "first time" CTx patients: 9 were < 3 y.o.; 9 were ≥ 3 < 10 y.o.; 13 were ≥ 10 < 14 years; and, 9 were ≥ 14 years old. Males comprised 58%, females 42%. Diagnoses were: congenital heart disease (CHD) in 35%; idiopathic cardiomyopathy 30%; viral cardiomyopathy 16%; familial hyperlipidemia 5%; congenital cardiomyopathy 5%; and a miscellaneous group 8%. All patients were NYHA functional Class 4. Fourteen were inpatients, 13 in the ICU; 11/13 required one or more inotropic agents & mechanical ventilatory support. One child was placed on ECMO prior to CTx. The remaining 24 children came from home, so were considered to have "full stomachs". Thirteen patients received a "rapid sequence" induction with either thiopental (3/13), etomidate (3/13), or ketamine (7/13). The other 17 patients were induced with high-dose narcotics. Aside from those already on inotropes, four children required pressors during the prebypass period. All were maintained with O_2/N_2 mixtures, high-dose narcotics, amnestics and muscle relaxants. Twelve patients also received isoflurane. After bypass, 55% required inotropes; 9% needed isoproterenol to support heart rate, and 5% required pacing. PGE_1 infusions were used in 3 patients to treat pulmonary hypertension. The incidence of postoperative bleeding was low (2%); only one mediastinal re-exploration was noted.

Discussion: For adults, ischemic cardiomyopathy is the major indication for CTx (3, 4) while in this series of children, CHD was the most common indication. A large proportion of our children were preterminal at the time of transplant, since 34% required vasopressors & ventilatory support. This contrasts with only 10-14% in adults (4). In adults, mortal illness prior to CTx does not predict outcome (5) but this issue has yet to be addressed in children.

References: 1. Trans Proc 20:743, 1988; 2. J Heart Trans 8:20, 1989; 3. Ann Thorac Surg 41:126, 1986; 4. Br J Anaesth 58:1367, 1986; 5. Heart Trans 4:489, 1985.

S98

Title: COMPARISON OF NORMAL SALINE AND NORMOSOL FOR INTRAOPERATIVE FLUID THERAPY: ACID-BASE EFFECTS

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Introduction: The choice of crystalloid therapy for intraoperative volume management includes a variety of isotonic solutions. "Physiologic" preparations that include potassium, calcium and/or magnesium, and bicarbonate precursors (acetate, lactate) are frequently preferred. Beyond this, there is very little literature to support the use of physiologic solutions over normal saline. We compared the acid base effect of normal saline (NSS) and normosol(NMSL).

Methods: We reviewed the charts of 247 consecutive patients who had major surgical procedures with arterial lines in place. 133 patients received NMSL as their primary crystalloid, supplemented with normal saline for packed cell reconstitution. 114 patients received NSS as their only crystalloid. The use of blood products and hetastarch were left to the discretion of the clinician. Sodium bicarbonate was administered for a metabolic acidosis,defined as a pH and serum bicarbonate that had decreased by at least .10 and 7 meq, respectively, in the face of an unchanged pCO_2. We evaluated each case for estimated blood loss(EBL), length of case(LOC), total fluid administered, arterial blood gas analysis, and confounding causes of acidosis.

Results: The mix of surgical procedures,the LOC, EBL, and total fluid was similar between groups.(Table 1). The patients receiving NMSL had a statistically significant decreased incidence of developing a metabolic acidosis.(Fisher's exact test, p= .0001).(Table 2)

Table 1 All patients; mean value (+/- SE)

Crystalloid	**EBL-cc**	**Total fluids-cc**	**LOC-hr**
NMSL	2357 (215)	10758 (643)	7.34 (.19)
NSS	2755 (281)	10699 (631)	7.25 (.21)

Table 2 Incidence of metabolic acidosis

Crystalloid	**# patients**	**# with met acid**	
NMSL	133	11	
NSS	114	34	* p = .0001

Discussion: Anesthesia textbooks and handbooks do not strongly support the use of one crystalloid solution over another. NSS should have similar hemodynamic effects as NMSL. However our data shows that the addition of acetate (NMSL) reduces the incidence of metabolic acidosis significantly. The cause of the acidosis is likely dilutional. No patients had serious or prolonged episodes of hypoxia or hypotension. We did not measure serum lactate levels, however.

Dilutional metabolic acidosis is caused by a rapid expansion of the extracellular space. Because the pCO2 will remain stable, the Henderson - Hasselbalch equation predicts an increase in hydrogen ion concentration under these circumstances(1). Interestingly, the description of dilutional metabolic acidosis is limited to animal work, and a single case report in humans(2). Whether the treatment of the resultant acidosis is necessary or efficacious is controversial.

References:
1. Kidney International 8; 279, 1975.
2. Southern Med Journal 83; 354, 1990.

S99

Title: ADENOSINE AND ITS ANALOGS INHIBIT RELEASE OF $[^3H]$-NOREPINEPHRINE FROM GUINEA PIG RIGHT ATRIA

Authors: F.F. Foldes, M.D., O. Nagano, M.D., Y. Ohta, M.D., H. Nagashima, M.D. and E.S. Vizi, M.D.

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Introduction: Adenosine, 2-chloroadenosine (CADO) and 5'N-ethylcarboxamidoadenosine (NECA) decrease the evoked release of acetylcholine at the neuromuscular junction of mice.[1] In the present study the effect of adenosine and its derivatives was investigated on the evoked release of norepinephrine (NE) from isolated right atria of guinea pigs (g.p.) $[^3H]$-NE.

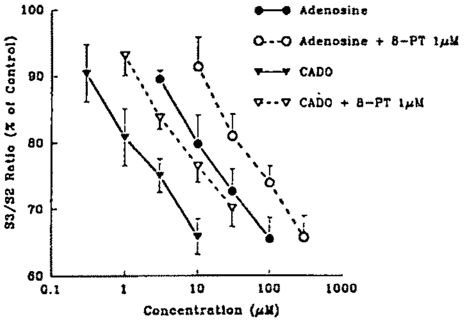
Methods. Right atria g.p. were loaded with $[^3H]$-NE, and superfused in 1.5 ml organ baths at 1 ml/min with Krebs' solution. Three min (3 ml) fractions of the superfusate were collected for 63 min. The preparations were electrically stimulated 3 times (S1, S2, S3) for 2 min at 2 Hz starting at the 9th, 27th and 45th min. The ratios of $[^3H]$-NE released by consecutive stimuli (S2/S1 or S3/S2) were calculated. Various compounds were added to the perfusion fluid 6 min after S2. Decrease of the S3/S2 ratios indicated inhibition, their increase, facilitation of $[^3H]$-NE release.

Results. Adenosine, CADO or NECA concentration dependently, inhibited the evoked release of $[^3H]$-NE (see figure; mean±SEM, n=4). Their potencies were: adenosine < CADO < NECA. 8-Phenyltheophylline (8-PT), an adenosine receptor antagonist,[2] competitively antagonized the inhibitory effect of adenosine and its derivatives on evoked release of $[^3H]$-NE (see figure).

Discussion. Adenosine, CADO and NECA, inhibited the evoked release of $[^3H]$-NE in g.p. right atria. Competitive antagonism of this effect by 8-PT indicates that the inhibition is mediated through adenosine receptors. The large amount of adenosine liberated from the myocardium in hypoxia[3] may inhibit NE release from the cardiac sympathetics and thereby offer protection against some of the complications (e.g. tachyarrhythmia) of myocardial hypoxia.

References.

1. Anesth Analg 72:S309, 1991
2. Life Sci 24:2475, 1979
3. Prog Neurobiol 27:319-349, 1986



S100

Title: HYPOXIC PULMONARY VASOCONSTRICTION IN SINGLE LUNG ANESTHESIA IN THE LATERAL POSITION IN ADULTS.

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Introduction During one lung anesthesia in the lateral position Hypoxic Pulmonary Vasoconstriction (HPV) may be important in attenuating Qs/Qt and maintaining PaO2[1,2]. HPV has not been clearly demonstrated in this situation. The aim of this ongoing study is to demonstrate HPV in single lung anaesthesia in the lateral position.

Methods With institutional approval and patient consent, 7 patients were anaesthetized with thiopental, midazolam, fentanyl, and pancuronium. A double lumen endotracheal tube was positioned with fibreoptic bronchoscopy, radial and pulmonary artery catheters were placed and the patient turned to the lateral position. There were four consecutive experimental stages: BASE: 2 lung ventilation (2LV), PRE: 1 lung ventilation (1LV), SNP: 1LV with sodium nitroprusside (SNP) infusion, and POST: 1LV with SNP discontinued. Data was recorded in each stage after stable conditions were achieved - all prior to surgery. Results were expressed as means ± SEM. Analysis included ANOVA and paired t-tests, with P<0.05 considered significant.

Results With 1LV PaO2 declined to 285 ± 42 mmHg (p<0.004) and the shunt increased to 29.02 ± 4.8% (p<0.03). With SNP infusion there was a significant further decrease in PaO2 and the QS/Qt tended to increase (p>0.05),(Table 1, Fig 1).

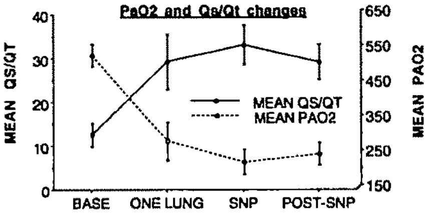
Discussion Assuming the 12% shunt during 2LV was equally distributed to each lung (6% in each lung) and 40% of cardiac output went to the non-dependent lung, then 34% of pulmonary blood flow was available for gas exchange in the non-dependent lung. With 1LV the increase from 12 to 29% was an increase of 17%. Therefore that portion of lung blood flow available for gas exchange was reduced by 50% with 1LV (17%/34%)- presumably by HPV. With SNP infusion the HPV response was 38% (34-21/34%) representing ablation of HPV by 24% (50-38/50%). We conclude 1: Shunt and PaO2 observed with 1LV in the lateral position are consistent with active HPV; the shunts are less than expected on the basis of gravity alone. 2: SNP infusion resulted in a small absolute increase in shunt fraction but a calculated HPV ablation of 24%.

References: 1. J Appl Physiol 59:189-196 2. Anesth 64:821-3

TABLE 1

	I Base. 2 LV	II Pre. 1 LV	III SNP 1 LV	IV Post 1 LV
MAP	81 ± 3	85.7 ± 4.4	65.1 ± 4	94.8 ± 5.9
MPAP	20.1 ± 2	19.5 ± 2.7	17 ± 2	19.4 ± 2
PAOP	12.8 ± 2	11.1 ± 1.9	8.8 ± 1.6	13.4 ± 2
CI	2.4 ± 0.4	2.45 ± 0.36	3.15 ± 0.46*	2.71 ± 0.61
PvO_2	57.3 ± 6.2	51.6 ± 4	50.8 ± 3	48.4 ± 4.7
SVR	1584 ± 355	1601 ± 280	931 ± 176	1718 ± 369
PVR	159.5 ± 35	165.53 ± 23	131 ± 22	103.8 ± 26
PaO_2	530.8 ± 42	285 ± 42 *	225 ± 47*	250 ± 43
Q_S/Q_T	12.3 ± 2.7	29 ± 6.1*	32.8± 4.5	28.9 ± 4.1*

* p<0.05



S101

Title: THE LARYNGEAL MASK: FIBREOPTIC DETECTION OF POSITIONING AND MEASUREMENTS OF ANESTHETIC GAS LEAKAGE

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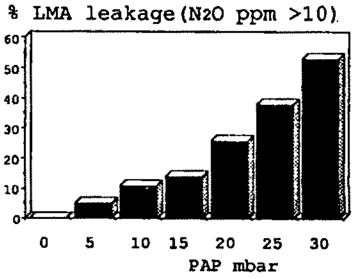
Introduction: The laryngeal mask airway (LMA) has been suggested to provide adequate ventilation with only minor gas leakage. The present study investigates position characteristics and waste anesthetic gas pollution by using the LMA.

Methods: Following informed consent 100 adult Patients (ASA I+II) undergoing general anesthesia for kidney stone lithothripsy were included in the study. Anesthesia was induced with 2 mg/kg propofol i.v. and 1.5 µg/kg fentanyl i.v. maintained with isoflurane plus nitrous oxide (N_2O) in O_2 (FiO_2: 0.3; 4.6 l /min) using IPPV with increasing peak airway pressure (PAP).

In all patients the position of the LMA in relation to arytenoid, epiglottis and laryngeal entrance was controlled by using a flexible fibrescope (Olympus BF Typ 10) and was documented by fibreoptic photography. The presence of LMA leakage was measured 20 cm above the head of the patient using a N_2O-infrared analyzer (Simrad Optronics, Norway). Adequate oxygenation was assessed using pulsoximetry.

Results: Successful insertion and sufficent ventilation conditions were possible in all patients. Immediately following insertion the position of the LMA was scored as central in 59%, dorsal in 8%,ventral in 4%,left in 9% and right 20%. Forced head flexion during insertion tended to produce a dorsal and deep position of the LMA; forced head reclination tended to produce a ventral position. In 13 patients, the lumen of the LMA was obstructed by more than 50 % due to downfolding of the epiglottis.There was no correlation between adequate ventilation, position of the LMA and PAP. In 15 patients, opening of the esophageal spincter was observed with PAP > 25 mbar.

Discussion: These results are consistent with previous studies where the use of the LMA was associated with adequate ventilation and tight seal. However, gas leakage and the risk of esophageal opening may occur with increasing PAP during IPPV. These data indicate, that LMA may suitable in fasted patients during IPPV, if PAP is below 25 mbar, but cannot be a substitute for an endotracheal tube.



S102

TITLE: COMPARISON OF THE EFFICACY OF DIFFERENT FIXED DOSES OF ESMOLOL TO ATTENUATE THE RESPONSES TO EMERGENCE AND EXTUBATION

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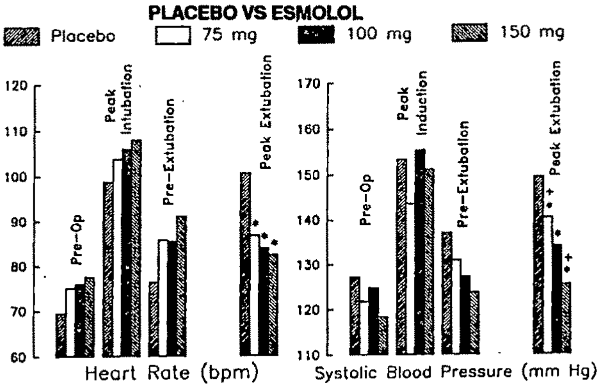
Emergence from general anesthesia and extubation have been shown to be potent stimuli resulting in significant increases in heart rate and blood pressure . The short-acting beta-blocker, Esmolol , given in an IV bolus, could be a clinically relevant method to control the transient hemodynamic effects of emergence and extubation.

Methods: After Institutional Review Board approval and informed consent 70 ASA I-II patients were enrolled in this double-blind randomized study and underwent a variety of general surgical procedures. Premedication consisted of 2 mg of midazolam. Anesthesia was induced with sodium thiopentothal, succinylcholine was given to facilitate intubation after defasiculation with curare. Lidocaine (1 mg/kg) was given prior to intubation. Fentanyl ($\leq$5 ug/kg) was given with induction and during the case. Anesthesia was maintained with isoflurane, vecuronium was used for neuromuscular blockade. This was reversed with neostigmine and glycopyrrolate at the end of surgery. At approximately one minute prior to extubation, patients were given either placebo, 75 mg, 100 mg or 150 mg of Esmolol. Patients were excluded if their heart rate was less than 60/min or their systolic blood pressure was less than 100 at the time of the study drug bolus. Data collected included: heart rate and blood pressure during induction and for the last 10 minutes of surgery through exiting the operating room, and continued through the PACU period. Also noted were the quality of extubation and any incidences of nausea or vomiting.

Results: Each dose significantly reduced heart rate and blood pressure in response to extubation. No significant difference was seen between the doses in ability to control the heart rate, while the 150 mg dose resulted in a significantly lower blood pressure than the 75 mg dose. In addition, the heart rate and blood pressure in response to intubation may forecast the untreated response to extubation.



* P < 0.05 from placebo + P < 0.05 between groups

Conclusions: Emergence from and extubation after general anesthesia can result in significant increases in heart rate and blood pressure. Esmolol given in fixed doses can attenuate these responses: heart rate can be controlled with a smaller dose than the blood pressure response.

S103

ASSESSMENT AND CHARACTERIZATION OF THE ANESTHETIC EFFECTS OF INTRAVENOUS ADENOSINE IN THE RABBIT

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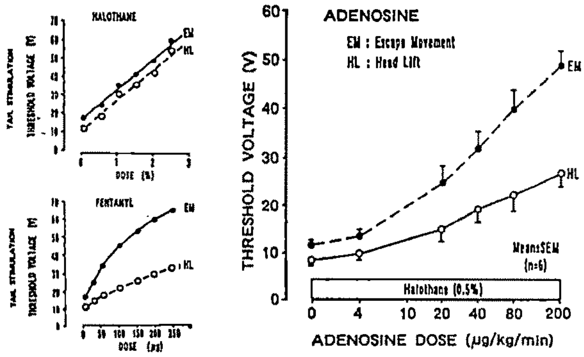
We evaluated and characterized the anesthetic activity of intravenous adenosine using the electrical tail stimulation method to test anesthetic antinociceptive effects as described in previous studies (1). Two distinct behavioral responses: a) Head Lift (HL) an arousal response by opening the eyes and lifting the head (hypnotic index), and b) Purposeful Escape Movement (EM) away from the noxious stimulus (analgesic index) were the end-points. Adenosine's anesthetic effects were compared with those of halothane, a volatile agent, and those of fentanyl, an analgesic drug.

Seventeen non-paralyzed, tracheotomized and cannulated rabbits (4-5 Kg) were placed in a hammock that allowed the animal's head and legs to be free to move. Baseline sedation was maintained with a sub-MAC dose of halothane (0.5 %) in O_2 spontaneously breathing subjects throughout the experiments. A pair of needle electrodes were placed in the shaved tail, and electrical current (1ms, 5Hz) was delivered increasing the intensities stepwisely (1 volt/sec) from a Grass S48 nerve stimulator.

The threshold responses for each drug were consistent and showed typical characteristic profiles for each drug. Increasing doses of halothane (n=6) consistently elevated the HL (hypnotic) and EM (analgesic) responses in a dose-dependent manner, whereas fentanyl (n=5) and adenosine (n=6) elevated EM responses but the HL responses remained low indicating analgesic properties (Fig.). Adenosine effectively blocked the hemodynamic responses to noxious stimulation and maintained normal respiratory and blood gas parameters. On the other hand, fentanyl depressed ventilation as the doses were increased. Continuous infusion of adenosine for prolonged times did not cause drug accumulation or respiratory depression; these unique pharmacological qualities of adenosine are desirable features in clinical anesthesia. Based on the animal behavioral and hemodynamic responses to noxious stimuli, adenosine may be categorized as a rapid acting anesthetic with primarily analgesic properties.

Fukunaga, AF et al: Assessing and characterizing the hypnotic and analgesic effects of anesthetic drugs. Annual Meeting of the ASA. San Francisco, 1991.



S104

Title: SUPERIOR SAGITTAL SINUS PRESSURE IN "UPRIGHT" PIGS. EFFECTS OF VOLUME LOAD AND AIRWAY PRESSURE

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Introduction: Craniotomies in the seated position are associated with the risk of venous air embolism (VAE); VAE may occur when venous pressure in the surgical field becomes subatmospheric. Preventive measures aim at elevating the pressure in cranial veins by means of intravascular volume expansion (Vol) and positive end-expiratory pressure ventilation (PEEP) [1]. Efficacy of these measures, however, remains speculative [2]. We have assessed effects of Vol and PEEP on superior sagittal sinus pressure (SSP), cerebral blood flow (CBF), oxigen saturation of superior sagittal sinus blood ($S_{ss}O_2$), intracranial pressure (ICP) and hemodynamic variables in an anesthetized, instrumented porcine model [3].

Methods: Six piglets (German landrace, 9±1 weeks, 25±2 kg) were premedicated (azaperone, 7.5 mg*kg^{-1} IM), anesthetized (piritramide, 2.5 mg*kg*h^{-1} + pancuronium, 0.4 mg*kg*h^{-1} IV), ventilated (40% O_2 in N_2O, etpCO_2 38±2 mmHg), instrumented, and positioned (prone on a tiltable table, head fixation in a stereotaxy frame with porus acusticus pins). Data were recorded at the following points of time: control 1 (t1), table tilt 35° head up (t2), PEEP (10 cmH_2O; t3), Vol (hydroxyethylstarch 6%, MW 40000, (HES) 10 ml*kg^{-1} over 5 min; t4), ZEEP (t5), control 2 (t6). Differences were analyzed (median of differences between points of time; Wilcoxon test) and assumed to be significant at $p \leq 0.05$.

Results: The head up position lowered SSP (-7 mmHg), ICP (-3 mmHg), CVP (-3 mmHg), PCWP (-5 mmHg), CBF (-10%) and cardiac output (-20%); $S_{ss}O_2$ did not change. PEEP increased mean airway pressure by 8 cmH_2O. CVP, ICP and SSP rose by 2 mmHg (n.s.). Volume administration increased these variables further (3/1/2 mmHg), CBF increased 30%. Returning from PEEP to ZEEP decreased CVP and ICP (-2 mmHg), SSP did not change. With repositioning to control, SSP, ICP, CVP and PCWP exceeded baseline values by 2-4 mmHg.

Discussion: The superior sagittal sinus is embedded in bony structures, preventing its collapse when transmural pressure approaches zero. Subatmospheric SSP allows air entrainment, when sinuses are opened surgically, making SSP the determinant of VAE risk. Head elevation decreased SSP linearly, as observed by others [4]; δ CBF indicated that the autoregulation of cerebral perfusion did not fully compensate the hydrostatic effect of positioning. In our study, PEEP increased MAWP semiquantitatively; effects on CVP, PCWP, ICP and SSP were less pronounced. Furthermore, effects of PEEP were overlapped by the adaptation of variables to the upright position, as shown by the insignificant effects of PEEP elimination. The response to volume administration was more pronounced, though insufficient to raise SSP to control. At t6, pressures were above baseline, reflecting the long halflife of HES. We conclude that: 1. PEEP of 10 cm does not increase SSP significantly. 2. Volume load increases SSP with or without PEEP, though not enough to compensate for effects of the upright position. 3. monitoring CVP, PCWP or ICP does not allow accurate estimation of SSP. Our data support administration of volume, but not PEEP, to provide some protection against VAE in the seated position.

References: [1] Anesth Analg 60:262, 1981. [2] Anesth Analg 62:287, 1983. [3] Anesth Analg 72:S127, 1991. [4] Anesthesiology 61:A386, 1984

S105

Title: EPIDURAL BUTORPHANOL DOES NOT REDUCE SIDE-EFFECTS FROM EPIDURAL MORPHINE POST-CESAREAN SECTION

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Introduction: Pruritus, nausea and respiratory depression are potential undesirable side-effects of epidural morphine (EM). The opioid agonist-antagonists can be successful in treating these when given systemically or by the epidural route. This study tests whether epidural butorphanol (EB) in various doses effectively reduces or eliminates the side-effects of EM without affecting analgesia after Cesarean section.

Methods: With institutional approval and patient consent women presenting for elective C-section under epidural anaesthesia were randomly assigned to one of four groups. All patients had a standard epidural technique. Gp A patients received 3mg EM and 1mg EB in 5ml. Gp B 3 mg EM and 2mg EB; Gp C 3mg EM and 3mg EB; Gp D 3mg EM and 2ml N saline. The opioids were injected 20 minutes after delivery. Each patient completed 10 cm visual analogue scales (VAS) for pain, satisfaction, nausea, itch and sedation pre-anaesthetic, 2,8, and 24 hours after the opioids were given. CO_2 challenge tests were done at the same time intervals. Minute ventilation (MV) and end-tidal CO_2 ($ETCO_2$) were recorded after breathing room air and then 5% CO_2 in air. This was a double-blinded investigation. Statistical analyses included Chi-square analysis, one-way analysis of variants and repeated measures ANOVA.

Results: Demographically the 4 groups, A (n=10), B (n=21), C(n=17) and D (n=23) were comparable in terms of age, height, weight, gestation, volume of local anesthetic and height of sensory level achieved. There were no significant differences between any of the groups at any of the assessments in pain scores or nausea, itch, and satisfaction scores. Gps A,B and C all had significantly higher sedation scores throughout the study compared to control Gp D. (See Table 1) There were no significant differences between groups in terms of time to first treatment of pain, nausea or itch, or in the CO_2 challenge test data.(See Table 2)

Conclusions: EB in doses of 1-3 mg failed to impart any advantage to women receiving 3mg EM after C-section. Some patients enjoyed the sedation that invariably occurred after EB while others felt that it affected their interaction with the newborn. These results differ from the findings of a previous study, where the authors concluded that EB may reduce the side-effects from EM.[1]

Reference 1. Lawhorn CD, McNitt JD, Fibuck EE, et al. Anesth Analg 1991, 72:53-7

Table 1. MEAN VAS SCORES
(0=best score)
(10=worst score)

TIME	1	2	3	4
PAIN				
A	0.55	2.73	2.20	1.7
B	0.61	2.45	3.43	2.69
C	0.38	2.71	2.35	1.57
D	0.54	0.76	2.17	3.07
p-value	0.903	0.0189	0.1409	0.0333
SEDATION				
A	0.72	6.95	5.22	2.00
B	1.37	6.51	6.58	2.73
C	0.85	7.15	6.22	1.82
D	0.88	4.22	3.41	1.80
p-value	0.487	0.0084	0.0007	0.4706

Table 2: CO_2 Challenge Test Results
% change in CO_2 responsiveness ↑ $VM/ETCO_2$ (litres/mmHg) measured at 2,8 and 24 hours post-op compared to pre-op baseline value:

	Mean Change in CO_2 Response		
Group	2 hr	8hr	24hr
A	↓26%	↓23%	↓40%
B	↓ 9%	↓11%	↓23%
C	↑ 2%	↓34%	↓41%
D	↓34%	↓46%	↓19%
p value	0.58	0.61	0.67

S106

TITLE: EFFECTS OF CLONIDINE AND LIDOCAINE ON AFTER HYPERPOLARIZATION OF RABBIT C-FIBERS

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Administration of clonidine together with lidocaine for peripheral nerve block prolongs local anesthesia (LA) and postoperative analgesia (1, 2). This effect might be mediated by a direct action of clonidine on the nerve. The present study examined the effect of clonidine and its interaction with lidocaine on C-fiber after hyperpolarization (AHP) in the vagal nerve preparation of the rabbit. Rabbit vagus nerves were desheathed and mounted in a sucrose-gap apparatus. The stimulation chamber was either perfused with Locke solution or lidocaine at a concentration which causes an approximately 40% reduction of the peak amplitude of the action potential ($5x10^{-4}$ M). Various concentrations of clonidine ($5x10^{-8}$ M to $5x10^{-3}$ M) were either added to the Locke or lidocaine solution. The preparation was stimulated by single supramaximal square wave pulses of 0.4 msec. AHP amplitude and prolongation of the AHP, calculated as the time of 50% recovery to baseline potential, were analyzed.

Lidocaine ($5x10^{-4}$ M) significantly prolonged the AHP (Table 1). This effect causes inhibition of nerve impulse propagation and thus increases LA action. Clonidine added to Locke solution at concentrations from $5x10^{-8}$ M to $5x10^{-3}$ M decreased the AHP at a concentration of $5x10^{-6}$ M, which translates into facilitation of nerve impulse propagation. AHP recovery time tended to increase with increasing clonidine concentrations. At equimolar concentrations, there was no difference from the increased AHP recovery time observed with lidocaine. In the presence of lidocaine, the inhibitory effect of clonidine ($5x10^{-6}$ M) on AHP amplitude was reversed, while a significant decrease in AHP amplitude was observed at the highest clonidine concentration. A small, but significant increase in AHP recovery, was observed with $5x10^{-5}$ M clonidine in the presence of lidocaine.

Present data indicate subtle effects of clonidine on the different components of the AHP and interaction with lidocaine, which may modify the propagation of action potentials. A LA-enhancing effect of clonidine mediated via the AHP should have been manifested by an increase in AHP amplitude and/or prolongation of recovery. However, a slight increase AHP recovery was only observed with clonidine in the presence of lidocaine ($5x10^{-4}$ M) at a concentration of $5x10^{-5}$ M. This effect most probably does not explain the prolongation of LA by clonidine in clinical peripheral nerve block, where clonidine is administered at an approximately 1000-fold lower concentration than lidocaine (1, 2).

Ref: 1) Anesthesiol.71:A644,1989; 2) Anesthesiol. 73: A821,1990

Table 1: Summary of experimental results

	LOCKE Pretreatment		LIDOCAINE Pretreatment	
Drug	AHP Amplitude	AHP Recovery	AHP Amplitude	AHP Recovery
Lidocaine				
$5x10^{-4}$ M	83.5 ± 8.6 (n=8)	424 ± 132† (n=8)		
Clonidine				
$5x10^{-8}$ M	95.4 ± 10 (n=5)	98.2 ± 3.3 (n=5)	93.4 ± 4.2 (n=4)	102 ± 6.4 (n=4)
$5x10^{-7}$ M	93.2 ± 6.4 (n=4)	102 ± 5.7 (n=4)	92.2 ± 2.2† (n=5)	106 ± 2.4 (n=5)
$5x10^{-6}$ M	71.6 ± 4.5† (n=6)	131 ± 29 (n=6)	96.0 ± 3.8* (n=5)	100 ± 5.3 (n=5)
$5x10^{-5}$ M	92.9 ± 12 (n=6)	123 ± 26 (n=6)	91.2 ± 3.8 (n=5)	106 ± 1.7† (n=5)
$5x10^{-4}$ M	121 ± 27 (n=8)	233 ± 81 (n=8)	78.1 ± 11 (n=4)	97.5 ± 4.2 (n=4)
$5x10^{-3}$ M	129 ± 39 (n=5)	208 ± 79 (n=5)	21.0 ± 3.1†* (n=4)	75.9 ± 12 (n=4)

Effects of clonidine or lidocaine expressed as % of pretreatment value (mean ± SE). *p<0.05 between group comparison, †p<0.05 within group comparison to pretreatment value.

S107

TITILE: COMPARISON BETWEEN THE ADMIXTURE OF CLONIDINE OR EPINEPHRINE TO LIDOCAINE IN AXILLARY PLEXUS BLOCK

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The addition of clonidine to local anesthetics for peripheral nerve block, has been shown to provide prolongation of the block and longer lasting analgesia than obtained with the addition of epinephrine (1, 2). As the local anesthetic-prolonging effect of clonidine might be due, similar to epinephrine, to vasoconstriction (3), the present study examined lidocaine plasma concentrations after an admixture of clonidine or epinephrine to lidocaine in axillary plexus block.

After informed consent and institutional approval, 33 patients (ASA I-II) scheduled for elective orthopedic surgery of the hand and wrist, were included in the study, which was conducted in a randomized, double-blind fashion. Axillary plexus block was performed in all patients with 40 ml of 1% lidocaine to which either 150 µg of clonidine (Group I, n=15) or 200 µg of epinephrine (Group II, n=18) were added. Sensory block was examined post-operatively every 30 min, until full recovery. Lidocaine plasma concentrations were measured until eight hours after the performance of the block. Post-operative analgesia was evaluated by visual analog scale (VAS 0-10) and by the consumption of pain medication until the next morning.

The two groups were similar with regard to the duration of sensory block and consumption of mefenamic acid. However, only 13.3 % of patients who had received clondine were painfree for more than 12 hrs, versus 61.1% of patients treated with epinephrine (Table 1). Lidocaine plasma concentrations showed significantly faster (Tmax) a higher peak (Cmax) with clonidine, than with epinephrine admixture. Total systemic lidocaine absorption (AUC) and plasma half-life (T1/2) of lidocaine did not differ between the groups (Table 2).

The admixture of clonidine to lidocaine in axillary plexus block produces comparable block duration as epinephrine, which is not due to local vasoconstriction. The prolongation of axillary plexus block by clonidine is most likely due to a direct action on the nerve, since a central analgesic effect of clonidine has previously been ruled out (1). Due to the absence of local vasoconstriction, toxic plasma concentrations of local anesthetics might be more readily obtained with a clonidine admixture. As postoperative analgesia is less favorable with clonidine, we see no advantage in the administration of clonidine, versus epinephrine, to local anesthetics for peripheral nerve block.

Table 1: Clinical Evaluation

	Clonidine (n=15)	Epinephrine (n=18)
Duration sensory block (min)	290 ± 62	303 ± 74
Mefenamic acid (g)	1.4 ± 0.8	1.0 ± 0.8
VAS = 0 >12 hrs (% patients)	13.3*	61.1

(mean ± SD,* P<0.05))

Table 2: Lidocaine Plasma Concentrations

	$T_{1/2}$	AUC	Cmax	Tmax
Clonidine	171.5	2334	10.29	23.70
(n=13)	± 35.8	± 507	± 2.96	± 9.30
Epinephrine	212.5	2116	6.90*	72.50*
(n=16)	± 74.7	± 537	± 1.71	± 56.2

(T1/2 = min; AUC = µmol x L^{-1}x 480 min; Cmax = µmol x L^{-1}; Tmax = min; mean ± SD, *P<0.05)

References: 1) Anesthesiology 73: A797, 1990; 2) Anesthesiology 71: A644, 1989; 3) J Cardiovasc Pharmacol 7 (Suppl 8):1-8, 1985

S108

Title: ANGIOTENSIN AND ADRENOCEPTORS IN THE HEMODYNAMIC RESPONSE TO AORTIC CROSSCLAMPING IN RATS

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Crossclamping of the thoracic aorta is associated with arterial hypertension, which is primarily due to an increase in impedance to aortic flow. However, some studies demonstrated an increase in concentrations of vasoactive compounds (e.g. renin-angiotensin and catecholamines) during aortic crossclamping.[1,2] The present study was designed to test the hypothesis that activation of adrenoceptors and/or renin-angiotensin system during crossclamping of the aorta play an important role in the overall hemodynamic response to aortic crossclamping.

Methods. The experiments were performed on anesthetized rats (n = 43) pretreated with saline (control group), or ACE inhibitor (Enalaprilat, 2 mg/kg), or α_1-adrenergic antagonist (prazosin, .5 mg/kg), or β-adrenergic antagonist (propranolol 5 mg/kg), or α_2-adrenergic antagonist (axpamezole 5 mg/kg). Mean arterial pressure (MAP) and cardiac output (CO), using an electromagnetic flowmeter, were measured throughout the experiments.

Results. Crossclamping of the thoracic aorta was associated with increases in MAP and systemic vascular resistance to different degrees: values of blood pressure in animals pretreated with ACE inhibitor or α_1-adrenergic antagonist were lower than control while the values in rats pretreated with β- or α_2-adrenergic antagonist were higher than control. CO was gradually declining in all groups of animals at approximately the same rate. However, the values of CO in the ACE inhibitor group were somewhat lower than in the animals treated with either adrenoceptor antagonist or saline.

Discussion and Conclusions. The study suggests that angiotensin is responsible for approximately half of the arterial hypertension developing during aortic crossclamping. Approximately 1/3 of the arterial hypertension is due to the activation of α-adrenergic receptors. Greater arterial hypertension in animals pretreated with β-adrenoceptor antagonist is possibly due to an unopposed effect of catecholamines on α_1-adrenergic receptors. Greater hypertension in rats pretreated with α_2-adrenergic antagonist apparently resulted from a combination of an increased overall sympathetic tone secondary to the administration of the α_2-adrenergic antagonist[3] and a further increase in sympathetic discharge secondary to crossclamping of the thoracic aorta.[4]

In conclusion, the present study confirms the posed hypothesis that the renin-angiotensin and sympathetic nervous systems play an important role in the hemodynamic response to crossclamping of the thoracic aorta.

References.

1. Can Anaesth Soc J 30: 480, 1983
2. Am J Physiol 259:H68, 1990
3. Br J Clin Pharmac 30:97, 1990
4. J Surg Res 34:97, 1983

S109

Title: CLINICAL EFFECTS AND PLASMA LEVELS FOLLOWING ORAL AND INTRAMUSCULAR PREMEDICATION WITH ATROPINE IN CHILDREN

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Introduction: Traditionally, infants and children are premedicated with intramuscular (i.m.) atropine (A) to prevent bradycardia during induction of anesthesia. Other desired effects are drying of the airways and reduction of salivation. This study was performed to compare the effects of i.m. versus oral (p.o.) A as preoperative medication with a control group without A.

Methods: After approval by the University Ethics Committee and informed consent of the parents, 45 children (age 2-10 years) were randomly assigned to 1 of 3 groups (n=15 per group). Group I received A, 0.02 mg/kg bodyweight (bw) i.m., 15 min prior to induction of anesthesia. Group II received A, 0.03 mg/kg bw p.o. with 10 ml of tab water, 20 min before induction. Group III did not receive A. The anesthetic regimen was standardized. Heart rate, rectal temperature, salivation, and A plasma levels (APL; measured by sub-selective radioreceptor assay) were determined before A, and at 15, 25, 45, 60, 90, 120 (no APL), and 150 min following A. Statistical evaluation used analysis of variance and t-test where appropriate.

Results: Compared to groups II and III, heart rate in group I increased significantly for the first 120 min after A. Bradycardia did not occur in any of the groups nor did temperature change. Antisialogogue effects were found only in group I at 25, 45, and 60 min after A. APL [1] (expressed as % of muscarine-2 receptor subtype occupancy) are shown in figure 1. Maximally 10-20 % of the receptors were occupied after oral A (peak at 60 min after A) compared to 60-70 % receptor occupancy after i.m. A (peak at 15 min after A).

Discussion: Our results indicate that A, 0.03 mg/kg bw p.o. is not equipotent to A, 0.02 mg/kg bw i.m.. Clinical effects cannot be detected unless at least 30 % of the receptors are occupied. Thus, an oral dose of 0.03 mg/kg bw is too low to obtain clinically desired effects. Since bradycardia did not occur even in patients of group III without A, the need for routine A premedication is doubtful. In addition, the relevance of reduced salivation in modern pediatric anesthesia is open to question. In conclusion, we recommend to omit routine A premedication in children.

References:

1. Naunyn-Schmiedeberg's Arch Pharmacol 338: 19-27, 1988

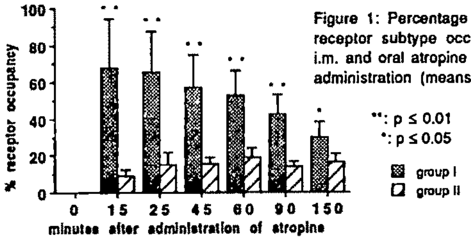

Figure 1: Percentage of muscarine-2 receptor subtype occupancy after i.m. and oral atropine administration (means ± SD)

S110

TITLE: PATIENT CONTROLLED SEDATION: A COMPARISON OF THREE TECHNIQUES DURING LOCAL ANESTHESIA

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Intraoperative patient-controlled sedation (PCS) has been reported to be a safe and effective technique.[1] We performed a prospective study to compare the safety and efficacy of PCS using propofol, midazolam or alfentanil during outpatient procedures under local anesthesia.

95 consenting ASA I-III adult patients undergoing ambulatory surgical procedures requiring sedation were studied according to an IRB-approved protocol. Patients were asked to complete a preoperative questionnaire in order to assess their need to "be in control", desired level of sedation, and degree of anxiety prior to the operation. All patients were premedicated with midazolam, 1 mg iv, and fentanyl, 50 µg iv, and randomly assigned to one of three treatment groups: Group I received alfentanil, 250 µg/ml; Group II received midazolam, 0.4 mg/ml; and Group III received propofol, 10 mg/ml. After applying nasal prongs (0_2 4L/min), all groups received a loading dose of 3 ml followed by a basal infusion of 5 ml/h which could be supplemented with 1 ml bolus doses "on demand" with a 3 min lockout using a Bard PCA device. To assess perioperative amnesia, patients were shown three sets of pictures: before and immediately after the operation, and upon arrival into the recovery room. Blood pressure, heart rate, and oxygen saturation values were recorded at 1-5 min intervals. Drug doses, recovery times and side effects were also determined (Means ± S.D.).

The three treatment groups were similar with regard to age, weight, sex, types of procedures, and ASA physical status. The duration of surgery was 49±28, 48±23, and 51±19 min in Groups I to III, respectively. The groups were also balanced with regard to patients' subjective desire to "be in control", desired level of sedation during the procedure, and baseline level of anxiety and alertness. Intraoperatively, adequate sedation was achieved in all three groups. The average drug administration rates for Groups I to III were 0.06±0.02, 0.10±0.03, and 2.37±0.77 mg/min, respectively. The total drug dosages were 2.70±1.15, 4.72±2.69, and 114±42 mg in Groups I to III, respectively. The propofol group required iv lidocaine more frequently due to venoirritation (39% versus 4% and 6% for groups I and II, respectively; $p < 0.05$), and the alfentanil group had an increased incidence of transient oxygen desaturation (<90%) (i.e.,28% versus 3% and 13% for groups II and III, respectively, $p<0.05$). However, no differences were noted with regard to discomfort or pain during local anesthetic injection or surgical incision. Finally, patients in each group reported comparable levels of anxiety, pain, and sedation during the operation.

Postoperatively, there was a higher incidence of nausea in the alfentanil group (29% versus 0% and 18% in groups II and III, respectively). No differences could be demonstrated with regard to level of anxiety in the PACU, postoperative confusion or drowsiness, or recovery times. Similarly, there were no differences noted with regard to patients' ability to recall pictures shown to them immediately after the operation and following arrival to the PACU. Although the mean number of bolus demands in each group was three times greater than the actual number of delivered bolus doses, all patients stated that they had no complaints with their sedation technique, and 97% stated that they would chose the same technique again in the future.

We conclude that self-administration of alfentanil, propofol, and midazolam using a PCA device is safe and effective during local anesthesia. The three drugs were equally acceptable in terms of patients' subjective assessment of sedation and level of satisfaction. However, propofol was associated with a higher incidence of pain on injection, while patients receiving alfentanil experienced a higher incidence of episodic desaturation intraoperatively and more nausea postoperatively.

[1]REFERENCE: Park W, Watkins P. Anesth Analg 1991; 72: 304-7.

S111

Title: ACUTE TOLERANCE TO FENTANYL AND MIDAZOLAM

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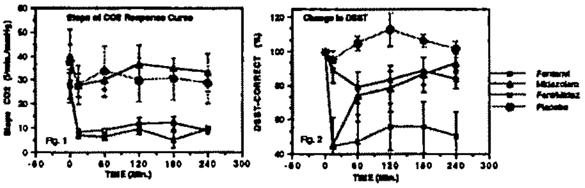
Introduction: The development of acute tolerance (hours) to Fentanyl (F) and Midazolam (M) has not been well characterized in man. We evaluated if acute tolerance occurs during administration of a constant concentration of each or a combination of both drugs.

Methods: Following IRB approval and written informed consent 5 healthy males 18-30 were studied. On 4 separate days at least 1 week apart, each volunteer received in double blind and random order either placebo (P), F (1.5 ng/ml), M (40 ng/ml) or a combination of F (1.5 ng/ml) and M (40 ng/ml) (F+M). M and F were administered by CACI, which enables a drug to be delivered to a desired concentration[1]. The volunteer was placed in a quiet room. Two intravenous lines were inserted, one for drug administration and a second in the opposite ante-cubital vein for measurement of plasma concentrations of fentanyl (RIA) and midazolam (Gas chromatography). The volunteers had the following tests performed: Ventilatory response to increasing CO_2 , DSST, and maximal analgesic tolerance to a spring loaded rod[2]. These were done at baseline, 15, 60, 120, 180 and 240 min. Blood samples were obtained for F and M concentrations at the same time periods. ANOVA was used to compare drugs. $p < 0.05$ was considered significant.

Results: CACI maintained the F and M levels constant over the 4 hours of the study. The slope of the CO2 response curve (Fig 1) was unaltered following drug in the P and M groups but was significantly and equally depressed in the F and F+M groups at all time periods. DSST % correct (Fig 2) and % complete showed an initial significant decrease in group M but this returned to baseline over the next 4 hours. In group F+M the DSST was significantly decreased for the entire 4 hours. Analgesic tolerance showed a similar pattern with no effect seen in groups P and M, a significant increase in analgesic tolerance in group F initially, but returning to baseline values by 4 hours. Analgesic tolerance was significantly increased for the full 4 hours in group F+M .

Discussion: The development of tolerance to the analgesic but not respiratory depressant action of fentanyl suggests differences in the opiate receptors in man responsible for these effects. The prevention of tolerance by the simultaneous administration of F and M has important clinical implications and may be due to an interaction between the opiate and benzodiazepine receptor.

1) Anesthesiology 73: 1082-90, 1990.
2) Anesth. Analg. 68: 302-307, 1989.



S112

TITLE: DOSE RESPONSE Of MIRFENTANIL (A3508) on RESPIRATORY RESPONSE to INCREASING CO2

AUTHORS: Glass PSA, Camporesi EM, Farinelli L, Leatherman N
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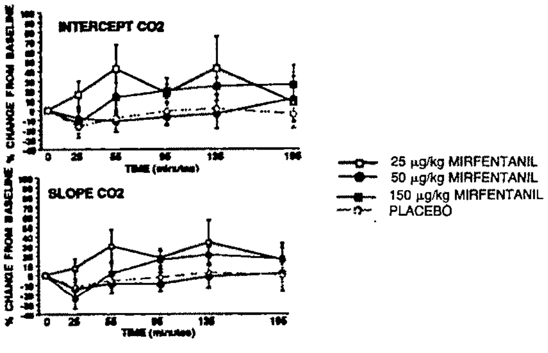
Introduction: Mirfentanil is a new piperidine derivative with unusual agonist antagonist activity and possibly greater effect at Mu1 than Mu2 receptors[1]. In human studies mirfentanil is 30 times less potent as an analgesic and 250 times less potent in increasing CO2 compared to fentanyl with a similar duration of action following a single dose[2]. This study evaluated the dose response of mirfentanil on ventilatory drive to increasing CO2.

Methods: Following IRB approval and written informed consent 12 healthy male volunteers were administered either 0, 25, 50 or 150 µg/kg mirfentanil as a single dose on 4 separate occasions at least 1 week apart. The ventilatory response to CO2 was measured using a bag in box system filled with 7.5% CO2. After 2 mixing breaths the CO2 was allowed to rise and minute ventilation was measured with a Screenmate pneumotachograph at 15 sec intervals. A CO2 challenge was performed prior to drug administration and repeated at 25,55, 95, 135 and 195 minutes. A baseline slope and intercept was calculated as the average of the 4 predrug runs. The percent change from this baseline was then calculated for each patient at each dosage level and at each time point.The data was analyzed by repeated measures and factorial ANOVA as appropriate. $p<0.05$ was considered significant.

Result: The change in slope and intercept produced by mirfentanil is illustrated in the figures.The highest dose of mirfentanil produced the greatest degree of respiratory depression at 25 min but this was not significantly different from placebo . The lowest dose of mirfentanil appeared to produce a degree of respiratory stimulation at 25 min. but this did not reach statistical significance

Discussion: With a potency one thirtieth of fentanyl, 50 and 150 µg/kg of mirfentanil would be expected to result in significant respiratory depression. These doses have been shown to produce moderate analgesia. The absence of significant respiratory depressant effects of mirfentanil within the dosage range studied is in agreement with previous animal studies and its unusual receptor profile[1]. Further studies are needed to establish mirfentanils clinical potential.

Refs:1) Drug Development Research 22,189-195,1991.
2)Anesthesiology 73,A835,1990,



S113

TITLE: PHARMACODYNAMIC COMPARISON OF GI87084B (GI), A NOVEL ULTRA-SHORT ACTING OPIOID, AND ALFENTANIL (ALF)

AUTHORS: P.S.A. Glass, M.D.*, H.D. Hardman, M.D.*, Y. Kamiyama, M.D*., K.H. Donn, Ph.D., D.J. Hermann, Pharm.D.

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INTRODUCTION GI is currently under investigation as an ultra-short acting analgesic. This study compared the rate of recovery of respiratory drive following a four hour infusion of GI to ALF.

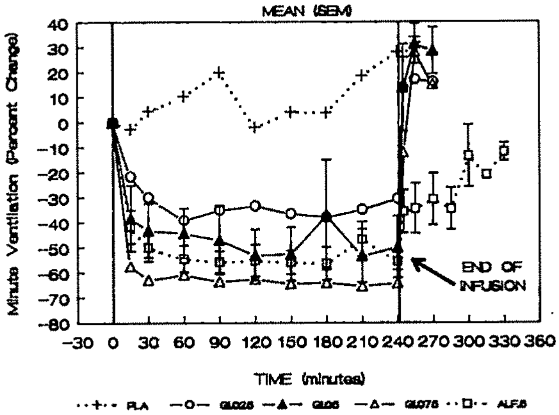
METHODS Volunteers received a four hour infusion of GI (0.025 mcg/kg/min, n=3; 0.05, n=6; 0.075, n=3), ALF (0.5 mcg/kg/min, n=5), or placebo (n=4). Respiratory drive was assessed at baseline, 15, 30, 60, 90, 120, 150, 180, 210, and 230 minutes during the infusion, and at 5, 15, and 30 minutes after the end of infusion or until values returned to baseline. Respiratory drive was evaluated by measuring minute ventilation (screen mate pneumotachograph) during a constant 7.5% CO_2 challenge (bag in box system).[1] Values recorded every 15 seconds between the fourth and fifth minute were averaged.

RESULTS (See Figure 1.) The average time to return to baseline was ≤8.3 (range 5-15) minutes for the three GI groups and 61 (range 5-90) minutes for the ALF group (p=0.002).

DISCUSSION These data show that GI is approximately 10 times more potent (mg:mg) than ALF during a steady state infusion. Recovery of respiratory drive after a four hour infusion of GI was extremely rapid and significantly faster than recovery following an equipotent infusion of ALF. Thus, GI could provide important clinical advantages.

REFERENCE 1. J.Appl.Physiol. 15:43-48; 1960.

FIGURE 1.
MINUTE VENTILATION versus TIME



S114

TITLE: EVALUATION OF POST CARDIOPULMONARY BYPASS ELECTROCARDIOGRAPHY VS. TRANSESOPHAGEAL ECHOCARDIOGRAPHY FOR THE PREDICTION OF PERIOPERATIVE MYOCARDIAL INFARCTION

AUTHORS: M. A. Gordon M.D., M. K. Urban M.D.,Ph.D, S.N. Harris M.D., T. O'Connor M.P.H., P. G.Barash M.D.

AFFILIATION: Dept. of Anesthesiology, Yale University School of Medicine,Yale-New Haven Hospital, New Haven,CT 0651

Introduction: Intraoperative myocardial ischemia detected by electrocardiographic (ECG) ST-segment analysis or transesophageal echocardiography (TEE) have both been associated with perioperative myocardial infarction (PMI)[1,2]. The impact of ECG ischemic changes and regional wall motion abnormalities (RWMA) occurring specifically during the post cardiopulmonary bypass (CPB) period needs to be better defined[3]. Using PMI as an outcome indicator, we evaluated the predictive value of post CPB ECG analysis and the appearance of RWMA.

Methods: Following HIC approval, forty-six (n=46) adult patients for elective CABG surgery were prospectively studied for post CPB myocardial ischemia and PMI. All patients were monitored with a peripheral and pulmonary artery catheter and received a standardized anesthetic of sufentanil 15-20 µg/kg and pancuronium. A Hewlett Packard computer processed ECG ST-segment analyzer was used to continuously monitor leads II and V5, which were recorded at two minute intervals. Ischemia was defined as new ST-segment deviation ≥1mm from baseline ECG. A TEE probe was positioned at midpapillary muscles to obtain a short-access view of the left ventricle. The cross-sectional image was divided into four segments: anterior, posterior, septal and lateral, and analyzed for RWMA independently by three investigators blinded to clinical outcome. Patients were followed for 72 hours post-operatively for ECG changes and elevations in CPK-MB fractions. TEE images were recorded for ten minutes upon separation from CPB or until the patient was hemodynamically stable, and again at chest closure. PMIs were defined as new ECG changes and CPK-MB > 80 units/L. Statistical analysis using Chi-Square with continuity correction were performed, and p <0.05 was considered significant.

Results: Post CPB ECG ST-segment changes were common, detected in 47% (22/46) of the patients, while post CPB RWMA were apparent in only 19% (9/46) of the patients. There were 4 PMIs, 3 of 4 (75%) had post CPB RWMA and 2 of 4 (50%) had post CPB ECG ischemic changes. However, two patients with PMIs were cardiac paced post CPB, therefore we were not able to detect ECG ischemia. Two of the 4 patients with PMI had both post CPB ECG ischemia and RWMA . The relationship of post CPB ECG ischemia with PMI had a low sensitivity (50%), specificity (50%- 21 false negatives), positive predictive value [PPV](8.7%) as well as no statistical association (p=0.67) (See table 1). However, the relationship of post CPB RWMA with PMI had greater sensitivity (75%), specificity (85.7%), PPV (33.3%) and were statistically significant (p=0.02) (See table 2).

Discussion: This data shows that the development of post CPB RWMA is a more powerful predictor of PMI than ECG ST-ischemic changes. Post CPB ECG ST-segment occur frequently, and are not statistically associated with cardiac morbidity (PMI). This is highlighted by the 2 patients with PMI who were paced, which precluded the diagnostic capability of ECG. In contrast, post CPB RWMA were detected throughout this period,even during pacing. Post CPB RWMA were both statistically associated with PMI and a useful predictor of PMI.

References:

1. Anasthesiology 71:16-25, 1989.
2. Anesthesia and Analgesia 66:1183-6, 1987
3. Circulation 82:1325-1334, 1990

Table 1
Postoperative MI vs. Post CPB ECG Ischemia

		MI		
		Yes	No	
ECG Ischemia	Yes	2	21	23
	No	2	21	23
		4	42	46

p = 0.501
Sensitivity = 50%
Specificity = 50%
Positive Predictive Value = 8.7%
Negative Predictive Value = 91%

Table 2
Postoperative MI vs. Post CPB RWMA

		MI		
		Yes	No	
RWMA	Yes	3	6	9
	No	1	36	37
		4	42	46

p = 0.024
Sensitivity = 75%
Specificity = 85.7%
Positive Predictive Value = 33.3%
Negative Predictive Value = 97.3%

S115

Title: DOSE RESPONSE TO MIVACURIUM IN INFANTS

Authors: N. G. Goudsouzian, M.D., A. Schwartz, C.R.N.A., G. Shorten, F.F.A.R.C.S.(I).
Affiliation: Department of Anesthesia, Harvard Medical School at the Massachusetts General Hospital, Boston, MA 02114.

Mivacurium is a short-acting non-depolarizing neuromuscular blocking agent. Previous studies have evaluated its dose response relationship in adults[1,2] and children.[3,4] This study evaluated the neuromuscular properties of mivacurium in infants 2 - 6 months.

Methods: The study was approved by our Human Studies Committee. Twenty-four infants, 2 - 6 months were studied during $N_2O:O_2$ and halothane anesthesia. The twitch response was evaluated by measuring the force of contraction of the thumb by a Grass FT-03 transducer. The ulnar nerve was stimulated supramaximally by surface electrodes at 2 Hz/2 sec repeated every 10 sec (train-of-four). As the infants were maintained by face mask, $N_2O:O_2$ and halothane (1%), mivacurium was administered at a dose of 0.04, 0.05 or 0.055 mg/kg. The twitch response, pulse rate and blood pressure were measured for at least 3 minutes and until the maximal neuromuscular response was obtained. Thereafter the infants were given an additional dose of mivacurium 0.1 mg/kg and then endotracheal intubation was performed. The Litchfield and Wilcoxon method was used for analyzing the data.

Results: None of the infants evaluated showed a significant change in heart rate or blood pressure and none developed a cutaneous flush. The neuromuscular effects of mivacurium are summarized below.

Dose mg/kg	n	% Depression of T_1 (mean ± SE)	Median
0.04	9	39 ± 14.1	15
0.05	9	66.4 ± 5.5	66
0.055	6	74 ± 7.1	75

Discussion: From the dose response analysis, the ED_{50} in infants 2 - 6 months during light halothane anesthesia was 0.045 mg/kg. This effective dose is slightly lower than that reported in children of 0.051 - 0.052 mg/kg[3,4] using the same anesthetic techniques and modes of stimulation.[1,2]

These small differences between infants (2 - 6 months), and children (2 - 12 y.), may have some theoretical significance but clinically should have a minimal effect since the recovery rates are faster in infants than in children. An interesting observation was that the maximum neuromuscular depression in infants occurred in less than 3 min whereas in children it occurred in 3.3 - 4.2 min.[3]

References:
1. Anesthesiology 68:723-732, 1988.
2. Anesthesiology 70:31-35, 1989.
3. Anesthesiology 70:237-242, 1989.
4. Anesth Analg 68:116-121, 1989.

S116

Title: MIVACURIUM INFUSION IN INFANTS

Authors: N. G. Goudsouzian, M.D., G. Shorten, F.F.A.R.C.S.(I)., A. Schwartz, C.R.N.A.
Affiliation: Department of Anesthesia, Harvard Medical School at the Massachusetts General Hospital, Boston, MA 02114.

Mivacurium is a short-acting, non-depolarizing neuromuscular blocking agent. Its short duration of action and non-cumulative properties make it ideal for continuous administration for maintaining a constant level of neuromuscular blockade. Previous studies have evaluated infusion of mivacurium on adults and children.[1,2]

Methods: The study was approved by our Human Studies Committee and parental consent was obtained. Fourteen infants (2.5 - 11 months) were anesthetized with $N_2O:O_2$ and halothane (1%). The twitch response was evaluated by measuring the force of contraction of the thumb by a Grass FT-03 transducer. The ulnar nerve was stimulated supramaximally by surface electrodes at 2 Hz/2 sec repeated every 10 sec (train-of-four).

As the infants were recovering from the initial dose of mivacurium (0.14 - 0.155 mg/kg), the mivacurium infusion was started at 14 ug/kg/min. According to the response of the infant, the infusion rate was adjusted to maintain a neuromuscular depression of 90 - 99% of control T_1 response. Data were analyzed by the Student's t-test.

Results: The infants in the present study required a mean (± SE) dose of 13.2 ± 1.1 ug/kg/min (range 8 - 24) of mivacurium to maintain 96.5 ± 0.9% depression of the first twitch of train-of-four. The mean duration of mivacurium infusion was 112 ± 15 (47 - 268) minutes. Based on a randomized table, eight infants were allowed to recover spontaneously. In these infants the twitch response returned to 95% of control in 7.4 ± 0.9 min, with a recovery index (25 - 75% of control, RI) of 2.9 ± 0.2 min. In the 6 patients that were reversed with 0.01 mg/kg atropine and 0.02 mg/kg neostigmine at a mean twitch response of 24.3 ± 2.6% of control, the recovery to 95% of control was in 3.2 ± 0.4 min (R.I. 2.1 ± 0.2).

Discussion and Conclusion: Compared to previous studies in children, infants had a tendency to require more mivacurium than children to maintain a similar degree of neuromuscular depression. More striking is their faster spontaneous recovery. Upon discontinuation of infusion, they recovered at almost twice the rate of children (2 - 12 y.).[1,2] Reversal with small doses of atropine and neostigmine accelerated the recovery to 95% by 4.2 min ($P < 0.005$), and the recovery index by 0.8 min ($P < 0.02$).

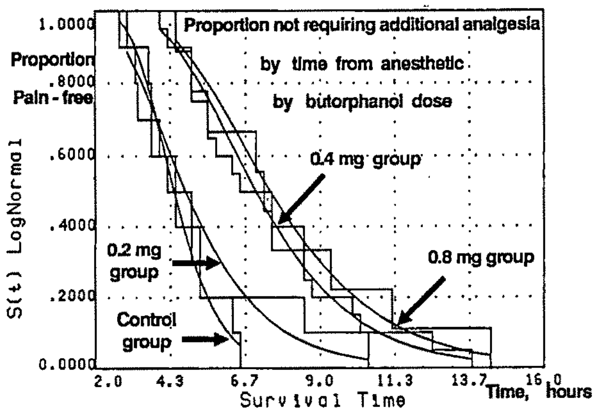
References:
1. Anesth Analg 71:16-22, 1990.
2. Br J Anaesth 63:520-524, 1989.

S117

Title:COMPLETE DOSE-RESPONSE OF SPINAL BUTORPHANOL

Authors:D.B. Gould, M.D., J.S. Smeltzer, M.D., S.B. Singer, D.O.
Affiliation: St. Louis Regional Medical Center, Departments of Anesthesiology and Obstetrics, 5535 Delmar Boulevard, St. Louis, MO 63112

Epidural morphine and butorphanol are equipotent analgesics[1]. Subarachnoid morphine has a fifty percent incidence of nausea and vomiting[2], commending alternatives. Butorphanol 0.4 mg mixed in spinal anesthetics has produced 8 to 16 hours of analgesia without side effects[3]. The entire range of dose-response to subarachnoid butorphanol in subjects receiving cesarean section by spinal anesthesia is reported here. A total of 49 patients were randomized in two studies among five groups: saline placebo; butorphanol 0.2 mg, 0.4 mg (two groups), and 0.8 mg. The study drug was combined with 15 mg bupivacaine in 8.25% dextrose and 0.3 mg epinephrine for spinal anesthesia. Continuous pulse oximetry was recorded (Mod 504, CSI, Waukesha, WI). Analgesia endpoint was receipt of additional analgesia for surgical pain. Subarachnoid butorphanol produced no episodes of oxyhemoglobin desaturation. Log duration of analgesia was normally distributed within groups. Butorphanol 0.4 mg prolonged analgesia ($p < .001$, figure, table). The group receiving 0.8 butorphanol did not have significantly longer analgesia than the 0.4 mg group ($p = .34$). This limit to the duration of action of spinal butorphanol may be a reflection of its high lipid solubility, which speeds entry into the neuraxis, with vascular redistribution. By manufacturer's data, the octanol/water partition coefficient (index of lipid solubility) of butorphanol tartrate at pH 7.5 is 180, 18 times that of morphine. Spinal butorphanol is effective, but of limited duration, for postoperative analgesia.



Outcome Characteristics by Dose

Dose Group	Mean duration	Individual 95% CI Lower	Individual 95% CI Upper	Difference from Cont.	Difference from 0.2	Difference from 0.4	Difference from 0.8
Control	4.46 hrs.	2.74 hrs.	7.24 hrs.	-	NS	***	**
0.2 mg.	4.82	2.24	10.37	NS	-	*	*
0.4 mg.	7.00	3.60	13.63	***	*	-	NS
0.8 mg.	7.45	3.69	15.05	**	*	NS	-

*$p < .05$, **$p < .01$, ***$p < .001$, by one-tailed t-test of log duration, higher dose produces longer duration.

References
1.Anesth Analg 66:887, 1987
2.Anesthesiology 70:742, 1989
3.Regional Anesth 7:73, 1984

S118

TITLE: DEVELOPMENT OF AN OPTICALLY SCANNED ANESTHESIA/QUALITY ASSESSMENT RECORD

AUTHORS: C.S. Graham, M.D., A. VanDerSpek, M.D., K.K. Tremper, Ph.D., M.D.
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Introduction: Anesthesia departments are currently faced with the clinical challenge of delivering safe, efficient anesthesia care as well as increasing administrative tasks. These tasks include accurate documentation of care and complications, capturing procedure, pharmacy and operating room charge data, satisfying professional and regulatory organization requirements for monitoring and assessing quality care and collection of case summary data for resident ABA annual reports.

Methods: We sought to collect necessary information while at the same time minimizing duplication of effort and avoiding cumbersome repetitive tasks. We have developed a comprehensive, multipurpose, optically scannable anesthesia/Quality Assessment (QA) record in an effort to standardize concurrent data collection on the approximately 25,000 cases per year done in five hospital locations involving anesthesiology faculty supervising residents, CRNAs and medical students.

Anesthesia records and Quality Assessment collecting tools were reviewed from multiple teaching institutions for content, layout and applicability. Anesthesia care providers were also polled for their preferences.

The prototype design is a double-paged record measuring 17 inches wide by 11 inches long. The left page includes a preoperative and postoperative anesthesia evaluation that remains in the patient's permanent record in addition to an optically scannable Postanesthesia QA Occurrence Screen. The occurrence screen tracks 26 late complications. Data is also collected by the hospital medical records department on 13 outcome indicators suggested by JCAHO[1] and reported back to the anesthesia department for later followup.

The opposite page is the permanent copy of the operating room anesthesia record. This record is optically scannable and includes the following blocks of information: patient demographics, procedure and diagnosis coding, anesthesia machine safety check, monitors, anesthetic technique and drugs used, airway management, special techniques, intravenous fluids/output record, position and protective measures, narcotics waste/return, transfer of patient care at the conclusion of the case and remarks. All blocks are clearly indicated on the record making use of scannable "bubbles" where possible. Carbon copies are disbursed to the pharmacy and billing office for processing.

The reverse side of the anesthesia record contains an optically scannable QA Occurrence Screen with ten blocks of demographic and background information in addition to 87 structure, process and outcome indicators. These indicators are tracked both in the operating room and Post Anesthesia Care Unit (PACU). The anesthesia care providers are responsible for completing the information concurrently and correcting any errors discovered in the data input phase.

All collected data is entered into a Macintosh SE via an optical scanner then downloaded to a 4th Dimension database in order to generate a monthly report tracking patterns and trends on a departmental and provider specific basis. Cases identified by monitoring serve as the basis of monthly departmental QA conferences.

Results: Preliminary results of the pilot study have shown a 90% compliance with the portions of the record that has been tested. We created a document that we believe will allow us to retrieve 100% of our QA and billing data and provide the least cumbersome system for our complex institution.

Reference: Joint Commission on Accreditation of Healthcare Organizations 1990.

S119

Title: LIPID VEHICLE PROLONGS EPIDURAL ANESTHESIA IN RABBITS

Authors: GJ Grant MD, L Langerman MD, M Zakowski MD, H Turndorf MD
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Introduction: Intrathecal local anesthetics in a lipid vehicle have been shown to prolong the pharmacological effect in animals[1]. We evaluated iophendylate as a lipid carrier on epidural anesthesia induced motor block of Procaine (P), Lidocaine (L) and Tetracaine(T).

Methods: Lumbar epidural catheters were implanted in 45 rabbits. P, L and T were added to normal saline or iophendylate to achieve 3 concentrations for each drug (Table). Preparations were compared with regard to duration and intensity of hind limb motor blockade using a modified Bromage scale. 100 µl/kg of each solution was injected and motor block was assessed. Each concentration was tested in 9 equal groups, and each animal served as its own control with the aqueous preparation tested 24 hours prior to the lipid formulation. Results (mean±SD) were analyzed using ANOVA for duration of block and X^2 for intensity of block.

Results: Maximal motor block intensity was greater for aqueous preparations of 2% L, 1% T and 2% T (p=0.0016). Prolongation (1.3-2.8x) of duration of motor block occurred with lipid preparations except for 2% L (Table).

Discussion: The prolonged duration and lesser intensity produced by lipid preparations implies a slow release of drug from the lipid depot. Our results suggest that lipid-drug formulations should be considered as a means of prolonging epidural anesthesia.

Reference: 1. Anesthesiology 74:105-107, 1991

Table. Motor block in minutes±1 SD.

DRUG	AQUEOUS	LIPID	p<0.05
PROC 1%	NONE	NONE	
PROC 2%	NONE	57±3	
PROC 4%	30±3	84±4	*
LIDO 1%	NONE	NONE	
LIDO 2%	41±4	39±4	
LIDO 4%	65±6	118±10	*
TETRA 0.5%	109±10	284±15	*
TETRA 1%	189±7	336±15	*
TETRA 2%	273±27	348±34	*

S120

Title: PAIN MANAGEMENT AFTER CESAREAN SECTION: SUFENTANIL PCEA VS. MORPHINE IV-PCA

Authors: JA Grass, MD, AP Harris, MD, NT Sakima, MD, RL Zuckerman, MD
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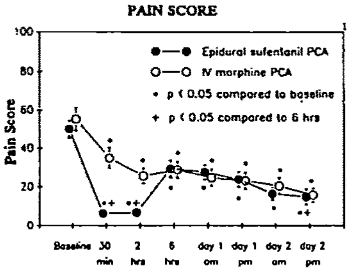
Introduction: Patient-controlled epidural analgesia (PCEA) may combine the superior quality of analgesia that has been shown with epidural morphine with the greater patient satisfaction of IV-PCA.[1,2] This prospective randomized study was designed to compare analgesia, side effects, and satisfaction of sufentanil PCEA with morphine IV-PCA.

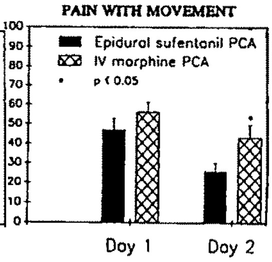
Methods: After IRB approval, 50 healthy term parturients (25 per group) were randomized to receive either PCEA or IV-PCA as outlined below after 2% lidocaine lumbar epidural anesthesia. Patients rated pain and sedation on a 10cm visual analog scale (VAS) at baseline, 30 min, 2 hrs, and 6 hrs on the day of C/S, and at 9:00 AM and 5:00 PM on POD 1 and 2. Daily VAS pain with movement scores were obtained and side effects were recorded. Statistical analysis was by analysis of variance, chi-square, and unpaired t-test where appropriate. $P < 0.05$ = significant.

SUFENTANIL PCEA PROTOCOL				MORPHINE IV-PCA PROTOCOL		
RR	Ward	For Pain		RR	Ward	For Pain
30 mcg		20 mcg	Bolus	5 mg		0.1 mg/kg
8 mcg	4 mcg	8 mcg	Dose	5 mg	1 mg	2 mg
10 min	10 min	10 min	Delay	5 min	10 min	10 min
6 mcg/hr	6 mcg/hr	6 mcg/hr	Basal	1 mg/hr	1 mg/hr	1 mg/hr
54 mcg/hr	30 mcg/hr	54 mcg/hr	Limit	30 mg/hr	7 mg/hr	13 mg/hr

Results: Pain scores at 30 min and 2 hrs and pain with movement on POD 2 were all lower in the PCEA group. Sedation was less in the PCEA group at 2 hrs and on POD 2. The incidence of pruritus requiring treatment was greater in the PCEA group on the day of C/S, whereas vomiting was more frequent in the IV-PCA group. Both groups rated satisfaction with their pain therapy equally very high.



PAIN SCORE



PAIN WITH MOVEMENT

Discussion: Both sufentanil PCEA and morphine IV-PCA provided very satisfactory analgesia after C/S. Superior analgesia in the early recovery period with less sedation with PCEA may have implications with respect to early maternal-neonatal bonding. Better pain relief with movement may have an impact on speed of recovery, morbidity, and associated costs.[3]

References: Harrison DM, et al.: ANES 68:454, 1988.
2) Eisenach JC, et al.: ANES 68:444, 1988.
3) Grass JA, et al.: REG ANES 15(1S):26, 1991.

S121

Title: A comparison of the residual effects of thiopental (T) and propofol (P) on newborn nutritive sucking behavior.

Authors: I. Gratz, G.E. Larijani, N. deCastro, B. Karayannis, A. Zubrow, M. Afshar, R.E. Kron.
Affiliation: Med. Coll. PA and Univ. PA

Introduction: It is generally accepted that some anesthetic agents readily cross the placenta. Since the newborn is susceptible to the CNS depressant effects of anesthetic agents, it is important to identify sensative markers of CNS organization and function. Newborn sucking is a complex process regulated by CNS and influenced by the effects of anesthesia. The purpose of this study was to compare the effects of T and P on newborn nutritive sucking during the first 2-3 days of life.

Methods: With IRB approval 16 healthy parturients scheduled for elective caesarean delivery under general anesthesia were randomly assigned to receive either T (2-4 mg/Kg) or P (1.5-2.5 mg/Kg) as induction agents. Anesthesia was maintained in all patients with 0.5% halothane and 50% N_2O in O_2 until the delivery of the newborn. The nutritive sucking was recorded for the initial 5 min of each feeding beginning at 2 hrs after birth and every 4 hrs until discharge. All newborns were fed with a calibrated nipple modified to allow for pressure measurement and deliver a standard flow of formula. Statistical analysis was by ANOVA with nesting to control for the within-patient variability. Means ± SD are reported. Differences were considered significant at $p < 0.05$.

Results: Two newborns failed to suck adequately on the modified nipple and were dropped from the study. Data from 14 newborns (7T, 7P) were available for analysis. The two groups were similar with respect to maternal and gestational age, birth weight, gender, induction to delivery time and Apgars at 1 & 5 min. There was a statistically significant difference between the groups for sucks per min and volume consumed over time. The number of sucks per min and volume consumed were significantly greater in the P group throughout the course of the study. No significant difference in the average peak negative pressure was observed.

Discussion: The study demonstrates that T and P differ significantly with respect to their effects on newborn nutritive sucking behavior. Recovery of sucking behavior appears to be significantly more rapid with P than with T. The results of this study are in partial accord with those of Kron et al,[1] who demonstrated prolonged depression of the CNS in newborns of patients receiving pentobarbital.

1. Pediatrics 1966, 37:1012-6

S122

Title: IN-VIVO OXYGEN SENSOR ACCURACY WITH A SELF-CENTERING ARTERIAL CATHETER

Authors: N. Gravenstein, MD*; E. Wegrzynowicz**; S.O. Heard, MD***; and M. Fink***
Affiliation: Depts. of Anesth., Univs. of *Fla. (32610-0254), **Iowa, and ***Massachusetts; Gainesville, FL 32610-0254

Inaccuracy in measurement of arterial oxygen tension (PaO_2) by in-vivo fiberoptic sensors may result partially from contact between fiberoptic sensor and blood vessel wall (1). We evaluated a stereotactic arterial catheter designed to inhibit contact between its attached sensor and the vessel.

With institutional review board approval and informed consent, a 20-ga radial artery catheter was placed in 19 volunteers. This catheter was then exchanged over a guidewire for the stereotactic 20-ga catheter prototype (CR Bard), through which an optical PaO_2 fiberoptic sensor fiber (CR Bard) was advanced. Each subject then breathed an inspired O_2 concentration of 100, 21 (ambient level), 35, 21, 80, 21, 50, and 21% for 1 h each. Blood was sampled anaerobically every 6 min and analyzed (IL 282 Analyzer). After catheterization of each subject, sensor and catheter tip locations within the radial artery were examined by ultrasonogram. Blood gas and sensor values for PaO_2 were compared by paired *t* test.

In 18 of 19 subjects, sensor and vessel wall were not in contact on ultrasonogram. PaO_2 values obtained by sensor and blood gas analysis correlated well with a linear regression (fig.): sensor PaO_2 = 0.989 x ABG PaO_2 + 0.647; $r = 0.96$.

This in-vivo catheter/sensor combination provides blood gas values that closely agree with in-vitro values and inhibits contact between sensor and vessel wall.

Reference
1. J Clin Monit 6:147, 1990.

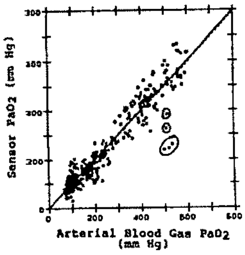


Fig. Correlation between PaO_2 values obtained by blood gas analysis and by a self-centering catheter with fiberoptic sensor. Eight of 646 data came from 1 subject with a small radial artery in which tangential contact occurred between sensor tip and vessel wall (circled data points; 3 points below 200 mmHg are not discernible). Dotted line: identity line; solid line: 0.989 x arterial blood gas value + 0.647.

S123

OVERSEAS TEACHING PROGRAM IN ANESTHESIOLOGY

Nicholas M. Greene, M.D.

The ASA-sponsored 5-year Overseas Teaching Program (OTP) was created to assist already established anesthesia training programs in countries so economically deprived that the potential of their own programs cannot be realized. The resulting shortage of anesthetists makes impossible to perform the amount of surgery that should and otherwise would be done.

The way OTP is designed is unique. (1) It centers on teaching only. (2) It is affiliated only with pre-existing structured anesthesia training programs. (3) Who is taught, what is taught and when it is taught is determined by the already established curriculum. (4) OTP volunteer teachers are present, one at a time, 12 months a year in each host institution. (5) OTP coverage is continuous for 4 years at one of the overseas locations, for 3 years at the other.

Volunteers must be ASA members who have completed residency training, who live in Canada or the USA, and who agree to serve overseas for 1 to 3 months. OTP provides round-trip tourist class air fare and a per diem. The host institution provides living accommodations.

The first OTP affiliation, that with the University of Zambia Medical School and its 1,400 bed hospital in Lusaka, was initiated on February 1, 1991. It is already successful. Volunteers returning from Lusaka are enthusiastic. So, too, are the Zambian faculty and staff. Indeed, Zambian MDs have, for the first time, enrolled in this university-based program. The second (and last) OTP affiliation is at the non-sectarian Kilimanjaro Christian Medical Center in Moshi, Tanzania. It started February 1, 1992.

S124

Title: COMPARISON OF THE ANTIEMETIC EFFECT OF I.V. DROPERIDOL GIVEN IN THE PACU VERSUS A DOUBLE DOSE REGIMEN IN CHILDREN HAVING TONSILLECTOMY AND ADENOIDECTOMY

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Introduction: Droperidol given at the time of induction of general anesthesia (GA) has been shown to effectively decrease the incidence of vomiting in children having tonsillectomy and adenoidectomy (T&A) from 71 to 46% (1). This is still a high incidence of postoperative emesis. We therefore designed this randomized double blind study to answer two questions:

1) Does a double dose regimen of droperidol, given at the time of induction of GA and in the PACU, increase the antiemetic effect?
2) Is a single dose of droperidol given in the PACU effective in reducing the incidence of postoperative vomiting?

Methods: After obtaining IRB approval and parental consent, 26 children ASA I-II aged 6 ± 1.5 (mean ± S.D.) years having T&A procedures were randomly assigned to 3 treatment groups: (I) I.V. droperidol 50 ug/kg given on induction of GA and 30 ug/kg given 1 hr after arriving in the PACU, (II) I.V. saline on induction of GA and I.V. droperidol 50 ug/kg 1 hr after arriving in the PACU, (III) I.V. saline both on induction of GA and 1 hr after arrival in the PACU. The patients did not receive a premedication. The anesthetic technique consisted of an inhalation induction using halothane and nitrous oxide in oxygen and intravenous morphine sulfate 0.1 mg/kg. Muscle relaxation was obtained using vecuronium bromide. All episodes of vomiting and the use of antiemetics were recorded from the time of arrival in the PACU until discharge from the hospital the following day. Differences between groups were evaluated using the student t-test. A p value <0.05 was considered statistically significant.

Results: There were no significant differences in age, weight, and sex between the three groups. Group II and III had a significantly higher incidence of vomiting on the floor when compared to group I (Table). Group I children had the lowest incidence of vomiting and those who vomited did so fewer times.

Discussion: Fifty ug/kg of droperidol given 1 hr after PACU admission did not prove to be an effective treatment for postoperative vomiting after T&A in children. In contrast, the double dose regimen was more effective - the total incidence of vomiting was reduced to 12.5% in this study population.

Table **Incidence of Postoperative Vomiting**

	Double Dose Regimen	PACU Dose	Saline
Group	I	II	III
Patients (n)	8	8	10
Vomiting(%)			
PACU	0	25	10
Floor	12.5	62.5*	50*
Total	12.5	87.5	60

P<0.05 versus Group I

References: 1. Grunwald Z, Schreiner MS, et al: Anesth. Analg. 1990; 70:S138

S125

Title: CHRONIC NALTREXONE MODULATES β-ENDORPHIN PEPTIDE AND mRNA LEVELS IN RAT CNS

Authors: HB Gutstein, MD, DM Bronstein, PhD, NC Day, PhD, KA Trujillo, PhD, H Akil, PhD

Affiliation: Dept. of Anesthesiology and Mental Health Research Institute, University of Michigan, Ann Arbor, MI 48109

Introduction: Scientists have long wondered if the tolerance and dependence induced by chronic narcotic administration are related to alterations in endogenous opioid systems. However, endogenous opioid levels have not been observed to change in response to chronic narcotic administration.[1] Recently, using mRNA levels and peptide release as dynamic indices of β-Endorphin (βE) system activity, we have shown that both parameters decrease in response to chronic morphine treatment.[2] This implies a dynamic downregulation of the βE system while maintaining constant peptide levels, and also suggests a possible role for βE in the cellular expression of opiate tolerance and/or dependence. The present study was undertaken to see if chronic opiate antagonist treatment had any effect on βE system activation or peptide levels in the rat CNS.
Methods: After institutional approval, 27 adult male Sprague-Dawley rats had either 10 or 30 mg naltrexone or placebo pellets implanted for 8 days. Animals were then sacrificed and βE levels in different brain regions were determined by radioimmunoassay. βE forms present were determined by molecular sieving using G-50 sephadex chromatography. mRNA levels of the βE precursor proopiomelanocortin (POMC) were determined by solution hybridization.
Results: Following naltrexone administration, total βE levels decreased by 20-50% in rostral CNS areas (arcuate nucleus, septum, thalamus, hypothalamus, and midbrain). The ratio of full length, opioid-active βE_{1-31} to the more processed, opioid-antagonistic βE_{1-27} and βE_{1-26} forms also increased in a dose-dependent manner. In more caudal CNS areas (medulla and spinal cord), βE levels did not change. POMC mRNA levels in the arcuate nucleus were elevated in treated animals compared to placebo controls.
Discussion: These data have been interpreted as evidence of upregulation of rostral βE systems in response to chronic naltrexone treatment. This suggests that βE levels decrease as a result of increased peptide release and mRNA levels increase due to a compensatory induction of POMC biosynthesis. The increased ratio of opioid agonist to antagonist forms seems to indicate that the rostral system also increases its relative opioid tone in response to chronic antagonist administration. Prior data suggesting differential regulation of rostral and caudal βE systems[3] also seem to be further supported by this study. These changes in βE systems appear to complement those observed with chronic narcotic administration and may have important implications for understanding the intrinsic mechanisms underlying narcotic tolerance and dependence.

References:
1. Fratta et. al., Nature, 268:452, 1977
2. Bronstein et. al., Brain Res. 519:102, 1990
3. Gutstein et. al., Anesthesiol., 73(3A):A683,1990

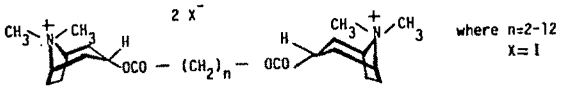
S126

Title: ANTICHOLINERGIC SPECTRUM OF ACTION OF DICARBOXYLIC ACID ESTERS OF TROPINE IN THE RAT

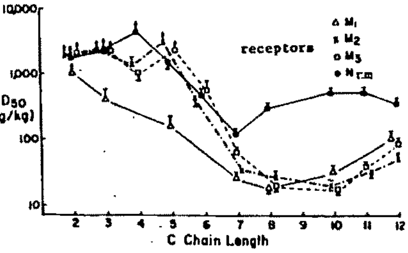
Authors: L Gyermek, M.D., N Nguyen, B.S., A Neumark, M.D., and C Lee, M.D.

Affiliation: Department of Anesthesiology, Harbor-UCLA Medical Center, Torrance, CA 90509

Introduction; Early studies on neuromuscular (nm) blocking dicarboxylic acid esters of tropine (1,2) have shown anticholinergic side effects. We explored the relationship between chemical structure and anticholinergic activity of the following tropine esters:



Methods: Male rats were anesthetized (Nembutal Na 50 mg/kg ip) and ventilated through tracheal cannula. Normocarbia, normothermia and hydration was maintained. Transduced arterial BP, heart rate and (nm) transmission (EMG responses to train-of-four stimuli) were monitored. Pharmacologic block of four responses were studied: I) Muscarinic M_1 receptor block: The spinal cord was transected at the atlanto-occipital level. The M_1 receptor stimulant action of 50-200 ug/kg McN 343, producing vasopressor response, was antagonized. II) M_2 receptor block: The vagus nerve was stimulated each 2 min. with trains of impulses (0.2 ms 10-15 Hz, 7-10 V). The bradycardic responses were antagonized. III) M_3 receptor block: Acetyl β-methylcholine (1-2 μg/kg) induced hypotensive responses were antagonized. IV) Nicotinic (N)nm receptor block: The magnitude of the first twitch of the train of four was determined. The blocking ED50 of each response was obtained on 4-7 rats/compound. Results: See figure.



Abscissa: Chain length (number of C atoms of the dicarboxylic acids). Ordinate: Potency (ED50 mcg/kg + SEM)

Discussion: 1) nm block peaks at interonium distances of 21 Å (C_2), 28.5 Å (C_7) and 36 Å (C_{12}) M receptor block increases with the chain length and reaches a maximum at 30-33 Å. Differences between optimal interonium distances in blocking N and M receptors suggest: a) The bond energy between the positively charged onium groups of these agents and the negatively charged groups of the N_{nm} receptor is too weak to alter the shape of the flexible polymethylene chain. 2) Because of the three peaks of N_{nm} blocking potency, distances between the anionic groups of the N_{nm} receptors may be about 7 Å. 3) Since with M receptors multiple binding at "anionic" as well as "esteratic" sites are required twinning of the corresponding, multiple-bonding groups of the blocking ligands at interonium distances less than 26-28 Å may produce steric hindrance. 4) The varying chain length affects M receptor subtype selectivity only with the shorter chain (C_2-C_5) derivatives.

References: 1. J. Pharm. Pharmacol 9:209, 1957.
2. Brit. J. Pharmacol 18:275, 1962.

S127

TITLE: THE USE OF A SPINAL FIELD BLOCK BEFORE EPIDURAL ANALGESIA FOR LABOR

AUTHORS: S. Halpern FRCPC., C. Huh, D. Djordjevic FRCPC.
AFFILIATION: Department of Anaesthesia, Women's College Hospital, University of Toronto, Toronto, Canada

Introduction
The spinal field block (SFB) has been reported to decrease acute and chronic back pain associated with spinal and epidural anesthesia in surgical patients (1). We examined, in a randomized, blinded fashion, the efficacy of the SFB in reducing both the pain of epidural needle insertion and the incidence of long term lumbar pain in parturients requesting epidural analgesia for labor.

Methods
The protocol was approved by the Research Ethics Committee at Women's College Hospital. After informed consent, 60 parturients requesting epidural analgesia for labor were randomly assigned to either the control group (Group C) or the study group (Group S). Before epidural needle insertion, patients in Group C received 1.5% lidocaine as an intradermal wheal and subcutaneous infiltration along the needle track. Patients in Group S receive the same treatment plus a SFB with 1.5% lidocaine, performed according to a previous protocol (1). A visual analog scale (VAS) was used by a blinded observer to quantitate back pain on needle insertion. The patient was again interviewed 48 to 72 hours post delivery concerning back symptoms, using the VAS. Six weeks post partum, a structured telephone interview was conducted. The patient was asked to rate the amount of back discomfort experienced at that time from 0 (none) to 10 (the worst pain ever). The sample size was determined using previous experience with the VAS on needle insertion. Data were analyzed using Mann-Whitney and Fisher's Exact tests as appropriate. A p value of < 0.05 was considered statistically significant.

Results
Three patients were eliminated from the study because of a break in protocol. There were 27 in Group C and 30 in Group S. The patients in both groups were demographically similar. There were no statistically significant differences between the groups in the amount of pain felt at the time of needle insertion, before discharge from hospital or six weeks after delivery. Four patients complained of severe pain (VAS=10) on needle insertion (3 in Group C, 1 in Group S). Only two patients reported prolonged back pain (score=8)–both in Group S.

Discussion
The SFB did not increase the comfort of the patient receiving epidural analgesia for labor. This may be because of the pain of the additional injections used to perform the block. The cause of prolonged back pain after epidural is multifactorial. It was postulated that inflammation and aseptic periosteitis or osteochondritis caused by local trauma may be reduced by SFB by inducing sympathetic blockade and promoting an increase in local blood flow (1). However, other causes of back pain would not be decreased using this technique. Pregnancy itself may contribute to low back pain because of mechanical and hormonal factors. We conclude that there is no advantage to the use of a SFB before epidural analgesia for labor pain.

References
1) Peng ATC, Behar S, Blancato LS. Reduction of postlumbar puncture backache by the use of field block anesthesia prior to lumbar puncture. Anesthesiology 63:227-228, 1985.

S128

TITLE: THE EFFECT OF KETAMINE HYDROCHLORIDE (KH) ON CEREBRAL BLOOD FLOW (CBF) DURING ACUTE HYPOXIA IN THE RAT

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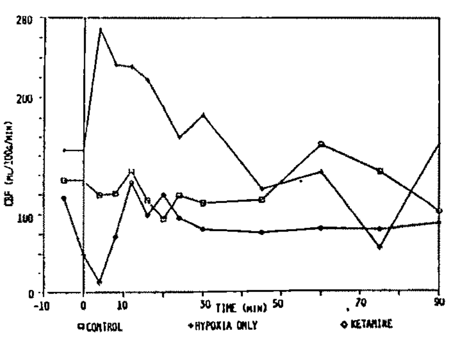
KH administered at low doses (5mg/kg) has been demonstrated to confer protective effects on the CNS during periods of acute hypoxia. In this study we examined the effect of low dose KH on CBF during an hypoxic insult.

Adult Sprague-Dawley rats were anesthetized with halothane, intubated and ventilated using a mixture of 40% FIO_2 and 1.5% halothane. $PaCO_2$ and PaO_2 were maintained within normal ranges. Arterial blood pressure, central venous pressure, heart rate, and arterial blood gases were monitored. Temperature was monitored with both intracranial and rectal probes and was maintained between 37°C and 39°C.

A hydrogen clearance electrode was inserted through a burr hole into the cerebral cortex to a depth of 1 mm for measurement of CBF. Pancuronium bromide (0.1 mg/kg) was administered IV, the halothane was decreased to 0.5% and the animals equilibrated for 15-30 minutes. Animals were divided into three groups. Group one served as the sham control (n=3). In group two, no pretreatment, (n=5) and group three, KH pretreatment 5 min prior to hypoxia (n=8), an eight minute period of hypoxia was induced by ventilation with an FIO_2 of 0.049. The ventilating mixture was then returned to the original levels. Physiological parameters were measured at four minute intervals before, during, and after the hypoxia.

Group two animals experienced a marked increase in CBF during the eight minute hypoxic period. This increase in CBF declined to prehypoxic levels over the first 30 minutes. Conversely, KH pretreated animals demonstrated a marked decrease in CBF during the eight minute hypoxic period with some animals registering no CBF at all. These animals experienced significant hyperperfusion eight minutes after hypoxia which subsequently decreased to pre-hypoxic levels over the next 30 minutes. The control group maintained approximately the same CBF throughout the experiment.

Low dose KH appears to substantially reduce CBF during periods of acute hypoxia, a response that is in contrast with autoregulatory impairment by KH. Part of the neuroprotective response to KH may involve a substantial reduction or complete cessation of CBF.



S129

TITLE: A STUDY OF THE PRIMING PRINCIPLE USING PIPECURONIUM

AUTHORS: David S. Handlin, M.D., Sandor Paskin, M.D. and Thomas Baker, M.S.
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Introduction. Priming has been demonstrated to effectively shorten the time between the intubating dose and satisfactory intubation conditions (1). This study confirmed the efficacy of vecuronium priming and determined that priming with pipecuronium (PIP) was effective when the time period between the priming and intubating doses was five minutes.

Methods. Approval of the Institutional Research Review Board was secured and informed consent was obtained from 52 patients ranging in age from 18 to 78 years with a mean age (±SD) of 40.0 ± 15.4 years, ASA physical status 1 and 2 undergoing general surgery. Patients with a history of a difficult intubation or on any medications affecting neuromuscular function were excluded. Anesthesia was induced with Na thiopental 2-3 mg/kg and fentanyl 2 μg/kg, maintained with O_2/N_2O and fentanyl. Patients were randomly divided into 4 groups of 13: 2 groups were administered PIP with 1 being primed, and 2 groups received vecuronium with 1 group being primed. The intubating doses were 0.07 mg/kg of PIP and 0.1 mg/kg of vecuronium. Patients being primed received 1/10 of the intubating dose. Five min later, the balance (9/10) of the intubating dose was given. The time from the intubating dose to intubation was measured. Intubation was rated on a scale of 0-4, with 4 being optimal, 3 good, 2 fair, 1 difficult and 0 impossible, and was based upon jaw relaxation, vocal cord relaxation and the patient's reaction to intubation (2).

Results. With patients who were primed, the mean time (±SEM) between the intubating dose and intubation for PIP was 102.5 ± 3.6 sec and for vecuronium was 97.6 ± 2.9 sec. In patients who were not primed these times were 163.2 ± 7.1 sec and 177.5 ± 6.2 sec, respectively, and are significantly different from their corresponding primed values. The intubation rating scores for primed patients were 3.4±0.1 and 3.6±0.2 respectively, and for non-primed patients were 3.5±0.2 and 3.6±.02, respectively. The intubation time and rating score for patients primed with vecuronium are similar to those reported elsewhere (1).

Discussion. Conflicting reports exist concerning the effectiveness of the priming principle (3). The present study demonstrates priming with PIP, a long acting muscle relaxant, is as effective as vecuronium. Many clinicians believe that priming does not work, particularly with long acting relaxants. The results of this study show otherwise: priming with PIP is effective and excellent intubation conditions can be achieved. Priming with PIP may be the anesthesia technique of choice in those situations where SCh is contraindicated and the duration of the surgical procedure is long.

References.

1. Anesth Analg 1989;68:S274.
2. Anesthesiology 1981;55:687-689.
3. Br J Anaesth 1989;63:1-3.

S130

Title: CARBOXYHEMOGLOBIN EFFECTS ON MIXED VENOUS OXIMETRY IN DOGS

Authors: MF Haney, MD, AR Tait, PhD, KK Tremper, MD
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Introduction. The performance of fiber-optic PA catheters for measuring mixed venous oxygen saturation in the presence of carboxyhemoglobin (COHb) has not been reported, though it has been estimated.[1] Hemoglobin species other than oxy- (O_2Hb) or reduced (Hb) are not discriminated by pulse or mixed venous oximeters.[2] Observations of COHb effects on pulse oximeter readings show that COHb is read to a significant degree as O_2Hb.[3] We hypothesized that the COHb effect on performance of the mixed venous saturation function of the Oximetrix catheters would be similar to that of pulse oximeters. It would not detect COHb, would overestimate the O_2Hb in the presence of COHb, and would sense COHb partly but not completely as O_2Hb.

Methods. Five 20-25 kg mongrel dogs were anesthetized with intravenous pentobarbital, inhaled halothane, nitrogen, and oxygen. A Femoral arterial catheter was placed, as well as a 7.5 F Abbott "Opticath" pulmonary artery catheter connected to and Oximetrix system display. Hemoglobin saturations were determined by a multi-wavelength co-oximeter calibrated for canine blood (Radiometer OSM3). Each data set included arterial and mixed venous blood samples, along with complete hemodynamic and respiratory gas data.

Results. COHb was interpreted partially, but not completely as O_2Hb (fig.1). To assess if the Oximetrix system was estimating functional SvO_2 ($FSvO_2$) accurately, the $FSvO_2$ was calculated ($FSvO_2$=venous O_2Hb/(O_2Hb+Hb)) and compared to the co-oximeter measurements in the presence of varying amounts of COHb. A best fit linear relationship for the figure 1 data was established with the equation y=−0.06+0.57x with r=0.96. The mean difference (x) between Oximetrix SvO_2 and $FSvO_2$ for all 88 data sets was calculated, with a mean x=−3.09 with a standard deviation of 6.55. A bias plot (fig. 2.) was constructed.

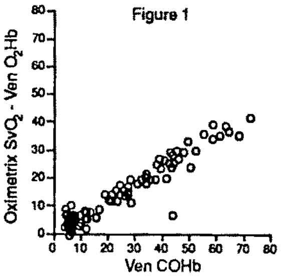
Figure 1

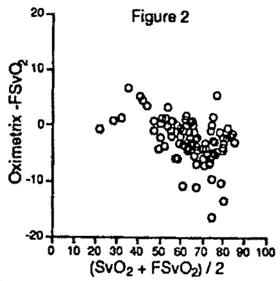
Figure 2

Discussion. Previous descriptions of the Oximetrix system and its ability to measure and calculate mixed venous O_2Hb percentage in the presence of COHb have suggested that COHb absorbs a small percentage of light within the same absorption spectra as hemoglobin and oxyhemoglobin. Our results show that the Oximetrix system estimates $FSvO_2$ in mixed venous blood, though it is unable to detect the presence of COHb, and reads COHb partially as O_2Hb (57% of COHb as O_2Hb). The reader would be cautioned to frequently measure mixed venous blood samples with a co-oximeter for an accurate SvO_2 if the patient is suspected of having COHb present.

1. Sperinde JM and Senelly KM. In Continuous Measurement of Blood Oxygen Saturation in the High Risk Patient. ed. Fahey PJ. Beach International, San Diego 1985, p 73
2. Barker SJ *et al.* *Anesthesiology* 1989:70, pp 112-7
3. Barker SJ and Tremper KK. *Anesthesiology* 1987:66, pp 677-9

S131

TITLE: EFFECT OF PROPOFOL ANESTHESIA ON THE INCIDENCE OF VOMITING AFTER STRABISMUS SURGERY IN CHILDREN

AUTHORS: R. Hannallah, M.D., J. Britton, M.D.,
P. Schafer, M.D., J. Norden, MSN
AFFILIATION: Children's National Medical Center and
George Washington University,
Washington, D.C.

This study evaluates the incidence of postoperative vomiting following strabismus surgery when propofol (vs. thiopental and/or halothane) are used for induction and maintenance of anesthesia in children.

Methods: Institutional approval and parental consent were obtained to evaluate propofol anesthesia in children (3-12 yrs old) scheduled for ambulatory surgery. This paper describes the findings in 35 patients who underwent strabismus surgery. No preoperative sedation or antiemetic prophylaxis were used. The children were randomized to receive one of four possible induction/maintenance combinations: group 1, propofol 3.0 $mg.kg^{-1}$/propofol infusion 50-500 $mcg.kg^{-1}.min^{-1}$; group 2, propofol/halothane 0.5-2%; group 3, thiopental 5 $mg.kg^{-1}$/halothane 0.5-2%; group 4, halothane for both induction and maintenance. Succinylcholine 1.5 $mg.kg^{-1}$ was used to facilitate tracheal intubation and N_2O/O_2 were used as the carrier gases in each case. Patients in group 1 also received vecuronium 0.1 $mg.kg^{-1}$. All maintenance drugs were titrated according to the clinical response of the patient to maintain BP ± 20% of baseline. The incidence of postoperative vomiting was compared among the four groups by a blinded observer using chi-square analysis.

Results: Patients' characteristics, duration of anesthesia and surgery were not significantly different among the 4 groups. The mean propofol dose used in group 1 patients was 222 $mcg.kg^{-1}.min^{-1}$. The percent of patients who experienced postoperative vomiting was 22.2% when propofol was used vs. 58.8% when it was not ($p < .03$). When propofol was administered for both induction and maintenance, the incidence of postoperative vomiting was 11%. There were no serious complications or adverse postoperative sequelae in any of the patients in the study.

Discussion: The incidence of postoperative vomiting following strabismus surgery in children who have not received some form of prophylactic antiemetic treatment has been reported to be as high as 85%(1). Droperidol(1) and metoclopramide(2) have been shown to significantly reduce vomiting in these patients. However, these drugs can result in drowsiness, extrapyramidal reactions and delayed hospital discharge.

Propofol anesthesia is associated with rapid recovery and a low incidence of postoperative vomiting(3). The findings in this study suggest that propofol may even have specific antiemetic properties that result in a lower incidence of vomiting following strabismus surgery than what has been previously reported when high dose droperidol or metoclopramide were used for prophylaxis(1,2). Further studies are needed to confirm the possible antiemetic properties of propofol.

References:

1. Anesthesiology 1983; 59:579
2. Anesthesiology 1990; 72:245
3. Br J Anaesth 1987; 59:654P

S132

TITLE: COMPARISON OF PROPOFOL AND THIOPENTAL FOR RAPID ANESTHESIA INDUCTION IN INFANTS

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L. Welborn, MD, J. Norden, MSN
AFFILIATION: Children's National Medical Center and
George Washington University, Washington, D.C.

This study compares the hemodynamic response to laryngoscopy and intubation as well as the awakening and recovery times when propofol or thiopental are used for rapid anesthesia induction in infants.

Methods: Following institutional approval and parental consent, 30 healthy full term infants (age 1-6 m.) scheduled to undergo inguinal hernia repair were studied. No preoperative medications were given. An intravenous catheter was inserted under N_2O analgesia and atropine 0.01 $mg.kg^{-1}$ was administered. Anesthesia induction was performed by one anesthesiologist who was not involved in the subsequent management of the child, using either propofol 3 $mg.kg^{-1}$(1), pentothal 5 $mg.kg^{-1}$(2) or saline (Control) by random assignment. Halothane 2% was immediately started and ventilation controlled. One minute later, succinylcholine 2 $mg.kg^{-1}$ was administered and followed by tracheal intubation. A second anesthesiologist, who was blinded to the induction sequence, managed the remainder of the anesthetic and adjusted the halothane concentration according to the child's clinical response. At the conclusion of surgery, bupivacaine 0.25% was infiltrated in the wound, anesthetic agents were discontinued, and the child's trachea was extubated when airway reflexes were regained. Changes in BP following induction, laryngoscopy and intubation as well as the awakening (extubation), recovery(3) and discharge times were compared among the 3 groups using ANOVA.

Results: Patients' characteristics were not significantly different among the 3 groups. The hemodynamic and recovery data are presented in the table:

Group	1 (Propofol)	2 (Thiopental)	3 (Halothane)	P(ANOVA)
n =	10	10	10	
BP preop	81.1±8.1	77.0±8.5	84.7±9.8	> .13
induction	84.4±13.0	96.8±13.3	92.8±14.2	> .13
intubation	87.8±11.4	103.4±13.4	108.1±15.3	< .006
preincision	66.6±11.8	81.4±14.2	73.2±16.8	> .09
incision	74.3±12.7	81.1±12.3	77.2±13.6	> .50
Anesth. time	44.0±6.5	50.3±7.2	47.9±11.8	> .30
Surg. time	26.2±5.8	27.6±5.4	28.8±11.0	> .76
Awakening (extub) time (min)	5.5±2.5	10.2±1.4	6.2±1.3	< .00001
Extub. End Tid. Hal %	.10±.03	.07±.04	.08±.02	.14
Recovery time	1.8±4.3	11.9±15.9	3.8±6.0	> .08
Discharge time	82.8±31.9	83.5±25.5	79.8±36.3	> .96

Discussion: Rapid anesthesia induction is indicated in infants at risk for vomiting or regurgitation, e.g. full stomach, reflux, etc. We studied infants undergoing hernia repair so that we have a uniform group that allows comparison of the response to various induction drugs in an elective controlled setting. Infants who received thiopental for iv induction demonstrated delayed awakening over those who received halothane alone. Infants who received propofol for induction showed no delay in awakening. Our results suggest that when rapid sequence intravenous induction is indicated in infants, propofol is much more effective in obtunding the hypertensive response to intubation and results in much more prompt awakening after short procedures than thiopental.

References:

1. Anesthesiology 1991; 74:4
2. Anesthesiology 1987; 67:104
3. Canad Anaesth Soc J 1975; 22:111

S133

ALFENTANIL ADMINISTERED PRIOR TO ENDOTRACHEAL SUCTIONING REDUCES CEREBRAL PERFUSION PRESSURE

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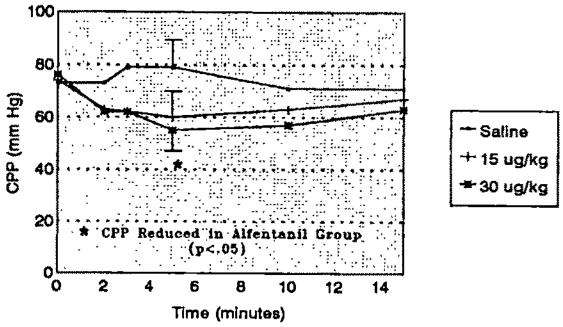
Introduction: We evaluated the effect of intravenous alfentanil on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) during endotracheal suctioning.
Methods: After human subject approval and consent, we studied seven mechanically ventilated patients recovering from closed head injury. Prior to endotracheal suctioning subjects received saline, alfentanil 15 mcg/kg, or alfentanil 30 mcg/kg. Subjects and investigators were blinded. ICP, MAP, HR, CVP, peak and plateau inspiratory pressures, and Glasgow Coma Score (GCS) were recorded. Data was evaluated using analysis of variance with repeated measures and is expressed as mean value ± standard error.
Results: Within 30 minutes of trials, GCS, ICP, and hemodynamic parameters returned to baseline. ICP was not different between control and drug treated groups. CPP was reduced ($p<.05$) in the alfentanil versus control group. Five minutes after alfentanil (3 minutes after suctioning), CPP was 78 ±8 mm Hg (Saline), 60 ±9 mm Hg (alfentanil 15 mcg/kg), and 55 ±6 mm Hg (alfentanil 30 mcg). Inspiratory pressures were not different between groups.
Discussion: CPP was reduced after alfentanil and endotracheal suctioning. Chest wall rigidity was not detected after alfentanil. GCS was not appreciably altered by low dose alfentanil administration; however, reduction of CPP in alfentanil treated patients suggests a reassessment of alfentanil for the neurosurgical patient. Alfentanil induced peripheral vasodilation is well described[1]. Further evaluation of potential cerebrovascular dilation may reveal mechanisms of alfentanil induced reduction of CPP.

Reference: White DA, Reitan JA, Nguyen DK, Thorup SJ. Decrease in vascular resistance in the isolated canine hindlimb after graded doses of alfentanil, fentanyl, and sufentanil. Anesth Analg 71:29-34, 1990.

Cerebral Perfusion Pressure
Alfentanil versus Control



S134

A NONLINEAR MODEL OF THE LUNG FOR DETERMINATION OF VENTILATORY TIME CONSTANTS IN ARDS

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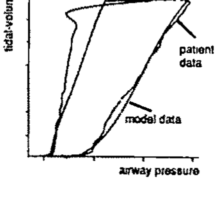
Introduction: A 2-compartmental nonlinear model for the simulation of mechanical characteristics of the lung during controlled artificial ventilation has been developed that is based on 3 important findings in ARDS:

- The model uses two different compartments (resistance R and compliance C) to simulate regional inhomogeneous ventilation.
- The compliance of each compartment is simulated in dependence of the intrapulmonary pressure using a nonlinear function (arctan). Alveolar recruitment as well as hyperinflation of the lung can be simulated by means of this function.
- The 2 compartments are seperated from each other by different time constants (R X C) allowing the simulation of "slow" and "fast" acting regions of the lung.

Methods: The model is based on 8 variables (R,C,pressure of maximal C and degree of nonlinearity for each compartment) by numerical integration (Runge Kutta) of its differential equations. The model can be applied to human respiratory mechanics using patient data generated by pneumotachography employing multivariable fit procedures. Using R and C time constants of the seperate compartments can be derived. In order to determine ventilatory time constants in ARDS, our model was used in 17 patients with ARDS on different levels of PEEP after approval by the University Ethics Committee. ARDS was defined and classified to mild and severe according to (1).

Figure 1



Results: The fit could be performed in almost all cases with a mean deviation between the patient´s and the model data of less than 1 cmH_2O. Figure 1 presents a typical pressure-volume-loop from a patient with the corresponding fitted model. Time constants of the 2 compartments found in our patients are shown in table 1.

Table 1: Time constants (median values in sec)

PEEP	Mild ARDS "slow"	Mild ARDS "fast"	Severe ARDS "slow"	Severe ARDS "fast"
0 cmH_2O	1.54	0.31	0.89	0.22
5 cmH_2O	0.93	0.25	0.76	0.17
10 cmH_2O	0.70	0.18	0.69	0.20
15 cmH_2O	1.18	0.18	0.51	0.24

Discussion: The time constants of the slow compartment found in the present study correspond precisely to the ones given in the literature (2). This is remarkable, because the classical approach of determining lung time constants is characterized by analyzing the exspiratory cycle. In contrast our model mainly fits to the inspiration and the plateau of the ventilatory cycle. Using this model, a non-invasive measure of the respiratory effects of mechanical ventilation in ARDS is provided that can be used to optimize the ventilation pattern. In stiff parts of the lung (fast compartment) this model shows that peak inspiratory pressure affects the lung tissue indicating that hyperinflation is likely. By adapting the respiration frequency to the time constants and decreasing tidal volume, damage of lung tissue caused by high inflation pressure can be avoided. The model provides clear data to support necessary adjustments of the ventilator.

References: 1. Am Rev Respir Dis 138:720 (1988)
2. Br J Anaesth 35:684 (1963)

S135

Title:

KETAMINE IN THE TREATMENT OF BRONCHOSPASM DURING MECHANICAL VENTILATION. A DOUBLE-BLIND PLACEBO CONTROLLED STUDY.

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Introduction: Ketamine possesses many characteristics which may participate in the reduction of an increased airway pressure. In several retrospective studies and case reports the positive effect of ketamine on acute severe asthma has been proposed.
The aim of our study was to evaluate the effect of ketamine on bronchospasms during mechanical ventilation.
Methods: We studied 14 mechanically ventilated patients with bronchospasm defined as thoracic compliance below 35 ml/cmH_2O and stetoscopic expiratory wheezing.
Midazolam 70 microg/kg BW was administered I.V. Patients were randomly allocated to a prospective, placebo-controlled, double-blind trial to receive either ketamine 1 mg/kg BW or saline placebo I.V.
Results. In the ketamine treated patients the pO_2 increased from 10.5 (0.5) kPa (Mean (SEM)) at $t_{(0\ min)}$ to 16.4 (2.7) kPa at $t_{(60\ min)}$ ($p<0.05$), while the pO_2 in the placebo treated patients remained unchanged. The pCO_2 increased from 5.6 (0.9) to 6.1 (0.9) kPa in the placebo group ($p<0.05$), while it was constant in the ketamine group. The levels of pulmonary stetoscopic bronchospasm improved immediately following the administration of ketamine from 2.3 (0.2) at $t_{(0\ min)}$ to 1.4 (0.3) at $t_{(5\ min)}$ ($p<0.05$), while no change was seen following administration of placebo.
The thoracic compliance was equal in the 2 groups at t_0 and remained unchanged during the study period
Discussion: We conclude that the use of ketamine may be considered in patients with severe bronchospasm refractory to maximal broncholytic therapy during ventilator treatment.

S136

TITLE:

MYOCARDIAL ISCHEMIA IN PATIENTS AWAITING CABG SURGERY: IS THERE A CIRCADIAN VARIATION?

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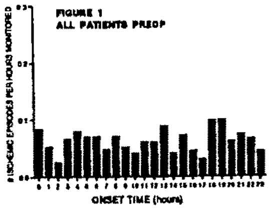
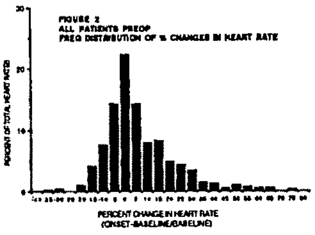
Introduction. A circadian rhythm of myocardial ischemia has been demonstrated in patients with Coronary Artery Disease (CAD). Knowledge of this diurnal variation is important in directing therapeutic decisions and in determining optimal monitoring times for patients with CAD. However, whether a similar periodicity of ischemic episodes exists in patients awaiting cardiac surgery is unknown. Therefore, we determined the temporal characteristics (circadian rhythm) of ECG ischemia using continuous Holter ECG monitoring in patients awaiting Coronary Artery Bypass Graft (CABG) surgery.
Methods. After institutional approval and informed consent was obtained, 186 patients scheduled for elective CABG surgery were studied. All patients were monitored with continuous ECG (Holter) leads CC5 and CM5 for 48 hours preoperatively. Holter tapes were read by two independent blinded investigators. A significant episode was defined as reversible ST-depression ≥ 0.1 mV from baseline at J+60ms, or ≥ 0.2 mV ST elevation at the J point, ≥ 1 min. For each patient, the number of ischemic episodes and their temporal distribution during the 24 hour period was determined. In addition, the heart rate at baseline, onset, and maximum ST deviation were recorded. These factors were then expressed graphically for each hour of the day. The relationship between heart rate and ischemia was determined using a two-tailed paired t-test.

Results. Of the 177 patients with interpretable Holter recordings, a total of 411 episodes were detected in 71 patients (40%) during the preoperative period. Analyzing the frequency of ischemic episodes in relation to time of day revealed a lack of circadian rhythm for all of the patients preoperatively (figure 1). Changes in heart rates of all patients were also found to be lacking any regular periodicity. Whether the patient received cardiac medications (beta blockers or calcium channel blockers) did not alter this finding. Of all ischemic episodes detected prior to surgery, only 111/411 (27%) were associated with an increase in heart rate (from baseline to onset) of >10% (figure 2).





Discussion. Our study demonstrated that:
1. Myocardial ischemia in patients awaiting cardiac surgery is common. However, we were unable to demonstrate a circadian rhythm in the distribution of ischemic episodes in contrast to that exhibited by ambulatory patients with chronic stable angina.
2. The majority of the ischemic episodes were found to be unrelated to a change in heart rate, suggesting that a primary decrease in myocardial oxygen supply may be an etiology of ischemic episodes.

S137

TITLE: **"CEREBRAL DYSFUNCTION" AFTER CARDIAC SURGERY IN ELDERLY PATIENTS**

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AFFILIATION: Departments of Anesthesiology* and Surgery#, Division of Cardiothoracic Surgery, Columbia University, New York, NY

Introduction: The reported incidence of "cerebral dysfunction" in patients undergoing open heart operations varies widely. This variance is probably due to anesthetic, surgical and cardiopulmonary bypass management; the tests used to assess cerebral function; and whether the average performance of a group or the number of individual patients with deficits (event rate) are used for statistical analysis. We are engaged in a study to reassess the incidence of "cerebral dysfunction" in elderly patients undergoing open heart operations using a neurological examination (NE) and a battery of eight psychometric tests (PMTs).

Methods: Following institutional approval and written informed consent, 9 patients were evaluated using NE and PMTs prior to surgery and postoperatively at two time points (within 5 to 13 days after surgery, and at follow up at least 6 weeks later) (see Table I for a list of the PMTs). All patients underwent open heart surgery and were placed on cardiopulmonary bypass (CPB) with a membrane oxygenator, an arterial line filter, and hypothermia to about 28°C. The anesthetic technique was the same for all patients. Almost all the surgery was performed by the same team of cardiovascular surgeons. A deficit was defined as an abnormal finding by NE or a decline of at least 25% in performance of one or more PMTs. Event rate comparisons were used to determine the incidence of "cerebral dysfunction" in two groups: Group A consisted of patients younger that 65 years old, and Group B, of patients 65 years or older. Patients with evidence of previous neurologic or psychologic illness were excluded.

Results: Groups A and B were comparable in terms of the duration of surgery, time of CPB, cross-clamp time, mean arterial blood pressure during CPB, amount of fentanyl and valium administered, and time to extubation. Event rate comparisons showed a statistically significant decline in performance using PMTs in Group B compared to Group A (Chi-square p=.0177): Group A has 11% abnormal on one PMT; Group B had 100% abnormal on one PMT, 44% abnormal on two PMTs, and 22% abnormal on three or more PMTs. The two tests that best discriminated normal from abnormal were perfomance on the Buschke Word List Learning Test (25% Group A, 100% Group B) and on the Grooved Peg Board (0 Group A, 60 % Group B). No deficits were determined in either group by NE.

Discussion: We have preliminary evidence of a higher incidence of "cerebral dysfunction" in elderly patients undergoing open heart surgery. These results are in general agreement with studies performed previously[1,2]; however, these previous studies were less complete in that they did not use both NE or PMTs, and were performed using bubble oxygenators and normothermia during CPB. Therefore, we consider our incidence of "cerebral dysfunction" a more accurate reflection of the current standard of care.

Table I: %age of patients with abnormalities

Psychometric Tests		Group A	Group B
Quantitative Mini-mental status		0	0
Trails	A	0	11%
	B	0	11%
Tapping	Dominant Hand	0	11%
	Nondominant Hand	0	0
Buschke Word List Learning		11%	44%
Grooved Peg Board	Dominant Hand	0	33%
	Nondominant Hand	0	33%

References:

1 Slogoff S, Girgis KZ, Keats AS. Anesth Analg 61:903-11, 1982.
2 Newman SP. Perfusion 4:93-100, 1989.

S138

Title: CONSISTENCY OF THE HEMODYNAMIC RESPONSE OF CANINES TO ENFLURANE AND ISOFLURANE AMONG SUBJECTS AND DAYS

Authors: WD Hoffman MD, LA Koev MD, MA Solomon MD, SM Banks PhD, I Yatsiv MD, JP Cobb MD, and C Natanson MD

Affiliation: Crit Care Med Dept, National Inst of Health, Bethesda, MD.

Introduction. We previously examined the effects of dose, anesthetic drug, and subject on the hemodynamic response of dogs to enflurane and isoflurane (J Appl Phys 7(5):2155-63). We found dose changes produced predictable hemodynamic responses that were similar in magnitude and direction for all dogs and both drugs. In contrast, drug changes produced variable hemodynamic responses that were significantly in opposite directions when comparing dogs. Because each dog was given each drug on a single day, we could not determine whether these opposite hemodynamic responses of dogs to enflurane and isoflurane would hold over several days (i.e.,whether dogs had inherently different responses to the two drugs). The present investigation examined this factor.

Methods. Using femoral and pulmonary arterial catheters and radionuclide heart scans, we determined mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), and left ventricular ejection fraction (LVEF). On each of 4 days (separated by at least 1 week), we evaluated six 2-year-old purpose-bread beagles (10-12 kg) given 2 anesthetics (enflurane, isoflurane), at 3 MAC doses (.75, 1.25, 1.75 MAC; end-tidal concentration). Orders of dogs, drugs, MAC doses, and days were randomly balanced. Variables were analyzed by ANOVA, with dog, drug, dose, day effects and interactions extracted.

Results. Within a day, the PCWP or CI response of one dog to isoflurane was significantly greater than its response to enflurane, whereas the corresponding response of at least one other dog was significantly different in the opposite direction (the response of the other dog to enflurane was greater than its response to isoflurane). In addition, for at least one dog, the PCWP or CI response on one day to isoflurane was significantly greater than its response to enflurane, whereas the corresponding response of this same dog on at least one other day was significantly different in the opposite direction (the response on the other day to enflurane was greater than its response to isoflurane). Thus, the difference in PCWP and CI responses to enflurane and isoflurane were opposite for at least 2 dogs on a single day and for at least 1 dog on a subsequent day.

For MAP and LVEF, enflurane (compared with isoflurane) produced a greater decrease (across all 6 dogs and 4 days). Within a day, at least one dog had a MAP or LVEF response to isoflurane and enflurane that was significantly greater than the mean response of the six dogs. In addition, at least one dog had a LVEF response to isoflurane and enflurane on one day that was significantly greater than the mean response of that same dog on other days. Thus, the MAP and LVEF response of dogs to different drugs were not opposite but differed significantly in magnitude for at least 2 dogs on a single day and for at least 1 dog on a subsequent day.

Discussion. Results of our previous study of dog, drug, and dose effects showed that differences in the hemodynamic responses to enflurane and isoflurane were inconsistent when comparing dogs. The present study examined differences in response of dogs to drugs on several days. These results show inconsistent hemodynamic responses to enflurane and isoflurane when comparing several dogs on individual days and individual dogs over several days. These data suggest that factors associated with day (such as level of autonomic function), and not only factors associated with the dog (such as genetic predisposition), make the difference in the hemodynamic response to enflurane and isoflurane inconsistent and not predictable in magnitude or direction.

S139

TITLE: ATROPINE AND MYOCARDIAL CONTRACTILITY DURING HALOTHANE ANESTHESIA IN CHILDREN

AUTHORS: H. Horigome, M.D. , M.H.Tsuji, M.D.* , M. Yamashita,M.D.*
AFFILIATION: Department of Pediatrics and Anesthesiology*, Ibaraki Children's Hospital, Mito, 311-41, Japan

Atropine effectively antagonizes the halothane-induced bradycardia in children[1] , but it is not investigated well whether atropine can improve ventricular functions in a dose-dependent fasion[2] . Left ventricular functions were evaluated echocardiographically following two different doses of atropine during halothane anesthesia in children.

Methods: The study was approved by the Ethics Committee of the hospital and parental informed consent was obtained . Thirty-four ASA I children , aged from 15 to 154 months, undergoing minor surgery were studied . No premedication was administered. General anesthesia was induced with inhalation of halothane/N_2O/O_2, and atropine 0.01mg(Gr.1,N=16) or 0.02mg/kg (Gr.2,N=18) was administered iv after the end-tidal halothane concentration had reached to 1.5%. Echocardiographic tracing was recorded at the following points ; pre-induction , end-tidal halothane 1.5% , and after atropine iv. Student's t-test was utilized for statistical anaysis, and p value less than 0.01 was considered significant.

Results: The patients in both study groups were comparable with regards to age, height, and weight.

After atropine, mVcf recovered from the depressed state by halothane,however,LVEDD,LVSF, LSTI remained unchanged in both groups. There were no differences in echocardiographic values between the two groups at any point except for mVcf after atropine.

	Preinduction ,	Halothane 1.5%,	Atropine iv
Left systolic time interval(LSTI)			
Gr.1	0.26 ± 0.04	0.30 ± 0.05*	0.30 ± 0.06
Gr.2	0.24 ± 0.04	0.30 ± 0.05*	0.30 ± 0.06
Left ventricular end-diastolic dimension{LVEDD(mm)}			
Gr.1	34.2 ± 4.5	35.4 ± 4.0*	35.4 ± 5.0
Gr.2	33.7 ± 3.5	35.0 ± 2.7*	35.1 ± 2.8
Left ventricular shortening fraction {LVSF (%)}			
Gr.1	34.2 ± 3.9	26.5 ± 4.7*	27.8 ± 4.9
Gr.2	34.8 ± 4.0	27.6 ± 4.9*	28.7 ± 5.0
Mean velocity of circumferencial fiber shortening { mVcf (circ/s) }			
Gr.1	1.31 ± 0.22	0.94 ± 0.16*	1.19 ± 0.19**
Gr.2	1.34 ± 0.23	0.98 ± 0.20*	1.31 ± 0.24**#

*:P<0.01(Preind.vs.Halo),**:p<0.01(Halo.vs.atropine)
#:P<0.01(Gr.1 vs. Gr.2),

Discussion: Atropine of both doses failed to improve left ventricular function indices except for rate-dependent index of mVcf.With atropine iv,heart rate does increase , but improvement of left ventricular functions cannot be expected even in larger doses.

References: 1.Anaesthesia 45:1088,1990.
2.Can J Anaesth 36: 295,1989.

S140

Title: THE EFFECT OF NITROUS OXIDE ON THE PROCESSED EEG USING APERIODIC ANALYSIS

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Affiliation: Dept. of Anaesthesia, Dalhousie University, Halifax, NS, Canada

Introduction: The processed EEG using aperiodic analysis (AP) has been used to quantitate anesthetic drug effect and to assess clinical anesthetic depth.[1,2] AP has potential advantages over the more conventional EEG waveform analysis using Fast Fourier Transformation (FFT), specifically the lack of assumption of stationarity and the ability to analyze an isoelectric EEG.[3] Nitrous oxide (N_2O) is a common anesthetic adjuvant. While its influence on the EEG has been controversial[4,5], its effect on the EEG processed by AP has not been studied. The goal of this study was to investigate whether N_2O produced a dose dependent effect on the processed EEG using AP.

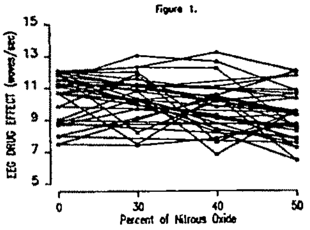
Methods: After obtaining IRB approval and informed consent, preliminary results from 4 healthy volunteers showed that there was excessive movement and laughing at N_2O concentrations of 60% and above. Accordingly, the N_2O concentrations studied are limited to 0-50% range. Twenty one volunteers were studied. Four bipolar channels of EEG were recorded continuously on FM tape for off-line analysis. After recording baseline EEG, N_2O was delivered at inspired concentration of 30%, 40% and 50% with O_2 sequentially in random order. Each concentration was maintained constant for a duration of 10 minutes. The EEG waveforms recorded during the tenth minute of each concentration were analyzed using AP (Lifescan®, Diatek, San Diego, CA). Total number of waves/sec (WS) was used as a descriptor of EEG N_2O drug effect. The data were analyzed using ANOVA with repeated measures and Bonferoni t-tests.

Results: None of the subjects lost consciousness during the study. The WS at different concentrations of N_2O are shown in Figure 1. The mean (± SD) WS at 0%, 30%, 40%, and 50% N_2O were 10.7 (1.4), 10.6 (1.5), 10.0 (1.8) and 9.27 (1.6) respectively. N_2O does have an effect on the WS (P<0.001, ANOVA with repeated measures) but only the EEG effect of 50% N_2O was significantly different (Bonferoni t-test) from the baseline.

Discussion: This study has demonstrated that in the absence of other anesthetics, 50% N_2O produces a small decrease in WS. However, with a large inter and intrasubject variability, this small effect (13%) may be clinically negligible. The WS has been shown to correlate well with plasma thiopental concentrations.[2] If N_2O contributes only a small additive EEG effect when it is used in combination with other anesthetic such as thiopental, then WS may prove to be a useful monitor of clinical anesthetic depth (anesthetic drug concentration).

References:(1) Clin Pharm Therap 48(5):544-554, 1990, (2) Anesthesiology 73(3A):A391, 1990, (3) J Pharmacokin Biopharm 18(5):459-481, 1990, (4) Anesthesiology 45:117-34, 1976, (5) Anesth Analg 60:283-8, 1981.

Figure 1.



S141

TITLE: PLACEMENT AND COMPLICATIONS OF DOUBLE-LUMEN ENDOTRACHEAL TUBES

AUTHORS: W.E. Hurford, M.D., P.H. Alfille, M.D., M.T. Ballin, M.D., E. Behringer, M.D., D.J. Cullen, M.D., K. Haspel, M.D., R.S. Wilson, M.D., and W.M. Zapol, M.D.
AFFILIATION: Dept. of Anesthesia, Massachusetts General Hospital, Boston, MA

Introduction: Proper placement techniques and complication rates of double-lumen endobronchial tubes (DLTs) remain controversial. We undertook this study to determine: 1) the success rate of "blind" endobronchial intubation using reusable (Leyland) and disposable (Rüsch, Sheridan) DLTs, 2) the types and frequency of placement errors, and 3) the influence of FOB on the complication rates of one-lung ventilation (OLV).

Methods: We prospectively analyzed DLT intubations occurring over a seven-month period on the Thoracic Anesthesia service of our hospital. Left and right reusable (Leyland) and disposable (Rüsch or Sheridan) DLTs were placed by residents working with staff anesthesiologists. The endobronchial tube selected, side of intubation, and use of FOB during DLT placement and the operation was left to the discretion of the staff anesthesiologist. The DLT used, number of attempts at blind intubation, use of FOB, findings at FOB if used during the intubation or operation, and complications occurring during the case (SpO2 < 90%, peak inflation pressure > 40 cm H2O, air trapping, less than ideal surgical conditions, and airway trauma) were recorded. All patients had their nonoperative bronchus intubated, received a volatile anesthetic and a nondepolarizing muscle relaxant, and were ventilated with 100% oxygen and a tidal volume of 10-15 ml/kg during OLV. Data were analyzed by the Fisher Exact test or Chi-square. A P value of < 0.05 was considered significant.

Results: 137 intubations were analyzed (57 right, 80 left; 54 reusable DLTs, 41 Rüsch disposable tubes, and 42 Sheridan tubes). Blind placement was successful more frequently when reusable tubes were used (78% vs. 41%, P = 0.018). The success rate of blind intubation was not influenced by the side intubated. Rüsch and Sheridan DLTs had similar success rates. 19% of reusable tubes and 42% of disposable tubes required position adjustments using FOB during placement (P = 0.025). During intubation, 22% of disposable tubes had been placed too far into the bronchus vs. none of the reusable tubes (P = 0.00025). The wrong side initially was intubated more commonly when left-sided tubes were used (15% vs. 4%, P = 0.039). Disposable tubes more commonly required readjustment using FOB during the operation (24% vs. 7%, P = 0.024).

One or more complications occurred in 23/137 patients (17%). The cause and frequency of specific complications were: decreased SaO2, 9% ; increased airway pressures, 8%; poor surgical conditions, 7%; air trapping, 1%, and airway trauma, 1%. The occurrence of complications was not influenced by the type of DLT chosen, the side intubated, or the use of FOB during placement. FOB was used to check DLT position in all but one case when complications occurred. In 13/23 (57%) patients who had complications, FOB was used to adjust the position of the DLT. In 9 (39%) patients, the tube position was correct and complications appeared due to underlying pulmonary pathology.

Discussion: "Blind" placement of DLTs is often successful and is not associated with an increased incidence of complications during OLV. Disposable tubes often are placed initially too far into the bronchus and require adjustment during placement and the operation more frequently than reusable DLTs. Complications, while common, were not related to the type of tube used, the side of placement, or the use of FOB during intubation. FOB was useful in confirming or adjusting DLT position when complications occurred during OLV.

S142

Title: PROPOFOL-NITROUS OXIDE ANESTHESIA DECREASES THE THERMOREGULATORY VASOCONSTRICTION THRESHOLD

Authors: J Hynson, M.D., DI Sessler, M.D., K Belani, M.D., D Washington, M.D., D Crankshaw, F.F.A.R.A.C.S., Ph.D., J McGuire, B.S., B Merrifield, B.A., A Moayeri, B.A. S Hudson, B.S.
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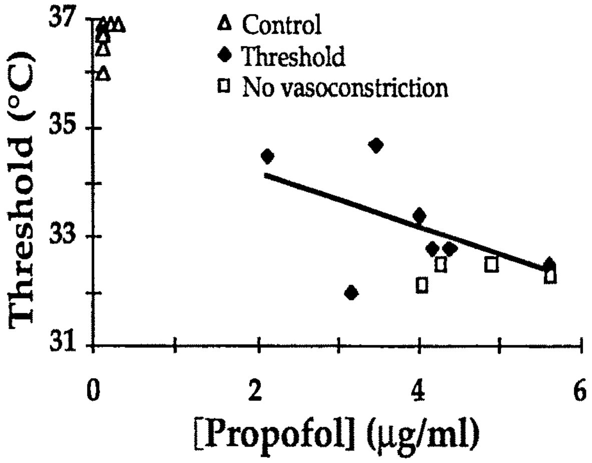
Volatile anesthetics[1] and N_2O/fentanyl[2] produce dose-dependent decreases in the threshold for thermoregulatory vasoconstriction. Intravenous anesthetics may not produce similar inhibition. We therefore evaluated thermoregulatory vasoconstriction in volunteers anesthetized with propofol and N_2O. Anesthesia was induced with propofol 2 mg/kg, and maintained with 60% N_2O and propofol 80-160 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Neuromuscular blockade was maintained with vecuronium. Volunteers were actively cooled using a circulating water blanket (set at 10°C). Arterial blood for propofol analysis was obtained at 15-min intervals. Thermoregulatory vasoconstriction was defined as a forearm - fingertip skin temperature gradient ≥ 4°C.[1] Significant thermoregulatory vasoconstriction was observed on 7 of 11 study days at tympanic membrane temperatures between 32.0-34.7°C with propofol levels of 2.1-5.6 μg/ml (Fig.). On the four remaining study days, cooling was discontinued before vasoconstriction at minimum central temperatures ranging from 32.1-32.7°C (propofol concentrations of 4.1-5.6 μg/ml). We conclude that general anesthesia with propofol and N_2O produces clinically significant thermoregulatory inhibition similar to other anesthetic agents.



Legend: The thermoregulatory threshold was decreased by N_2O/propofol anesthesia: Threshold = 35.1 - 0.8[Propofol], r = 0.53. The zero intercept of 35.1°C likely reflects thermoregulatory inhibition produced by 60% N_2O.

Reference:

1) Anesthesiology 72:822-827, 1990.
2) Anesthesiology 69:357-364, 1988.

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S143

Title: PHARMACODYNAMICS OF HIGH DOSE PROPOFOL IN HUMANS

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Introduction: The ideal anesthetic agent for neuroanesthesia should provide hemodynamic stability, cerebroprotective effects, and a short recovery time. Due to its pharmacodynamics propofol (P) could be superior to thiopental [1]. Therefore we investigated the effects of a high dose P infusion on hemodynamic variables and the electroencephalogram .(EEG).

Methods: The study was approved by the Ethic Committee. After written informed consent was obtained (n=10), a pulmonary artery catheter and an arterial line were inserted under local anesthesia. Online monitored parameters: heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), EEG (two channels, bipolar leads C3/P3, C4/P4, Fz), ECG, $p_{ET}CO_2$, FiO_2, temperature. Anesthesia: bolus dose of 1 mg kg^{-1} BW P, followed by an infusion of 20 mg kg BW h^{-1} P. Orotracheal intubation (vecuronium 0.1 mg kg^{-1} BW); controlled ventilation (FiO_2=1.0). After 30 min. the P infusion rate was reduced to 15 mg kg BW h^{-1} and terminated after 60 min. Lactated ringer solution was infused to keep PCWP constant. Blood samples for serum P- and lactate concentrations were drawn (0, 15, 30, 45 and 60 min.). Statistics: Friedmann- and Wilcoxon-Wilcox test ($p<0.05$; $\bar{x}$±SD).

Results: P produced the typical "burst suppression" pattern after 15.7±3.2 min. Significant decreases (maximum delta%) were found in HR (19%), MAP (20%), cardiac index (CI: 23%) and left ventricular stroke work index (LVSWI: 26%). There were no significant changes in RAP, PCWP, and systemic vascular resistance index (SVRI) (Table).

Discussion: P causes a maximum reduction of cerebral electric activity, metabolism and blood flow, whereas CO_2 reactivity is preserved [2]. In our patients MAP, CI and LVSWI decreased. Despite unchanged SVRI and fluid administration compensating the suggested decrease in preload by P, MAP decreased significantly. These facts suggest a negative inotropic mechanism [3]. The decrease of heart rate might be explained by the pronounced baroreflex inhibition [4] and may be considered beneficial concerning myocardial O_2 consumption. In conclusion, doses of P, sufficient to silence the EEG, can be administered with minimal hemodynamic risk, when the described guidelines are followed meticulously.

	Control	15 min	30 min	45 min	60 min
Σ Dose	0	1051±189	1399±251	1663±298	1926±346
Propofol	0	8.56±2.7	9.2±2.9	9.03±2.78	7.17±2
Lactate	0.91±0.55	0.99±0.53	0.99±0.46	0.94±0.5	0.92±0.44
HR	78±15	67±14	64±11*	63±10*	63±9*
MAP	98±10	85±15	84±16	82±13*	78±16*
RAP	5±2	6±3	6±2	7±2	7±3
PCWP	6±3	7±2	9±2	9±3	9±3
CI	3.0±0.5	2.3±0.7*	2.4±0.6	2.4±0.6	2.6±0.6
LVSWI	49.7±13.1	36.9±12.9*	38.8±15.5*	39.1±15.4	38.8±15.4
SVRI	2500±478	2956±844	2796±869	2607±699	2330±792

Table: ($\bar{x}$±SD, n=10, *=$p<0.05$ vs control). Cumulative propofol dose (Σ Dose;mg); P (μg/ml) and Lactate (mmol l^{-1}) plasma concentrations; heart rate (HR; beats/min); cardiac index (CI; l min^{-1} m^2); left ventricular stroke work index (LVSWI; g m m^2); systemic vascular resistance index (SVRI; dyn sec cm^{-5} m^2). Pressures (mm Hg): mean arterial (MAP); right atrial (RAP); pulmonary capillary wedge pressure (PCWP); Measuring points: control (=before); 15, 30, 45 and 60 minutes after start of the propofol infusion.

References:

1. Todd M, et al.: Anesth Analg 64:681-687,1985
2. Stephan H, et al.: Anaesthesist 36:60-65,1987
3. Mulier JP, et al.: Anesth Analg 72:28-35,1991
4. Cullen PM, et al.: Anesth Analg 66:1115-1120,1987

S144

Title: LABORATORY EVALUATION OF INTRAVENOUS FLUID WARMERS

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Introduction: Intravenous fluid warmers are often evaluated with models dissimilar from conditions usually used in the operating room. Therefore, we evaluated the DW-1000 (Gorman-Rupp), Hemokinetitherm (Dupaco), Fenwal BW-5 (Travenol), Flo Tem IIe (Datachem) and System 250 (Level 1) under simulated clinical conditions.

Methods: Three trials of lactated Ringer's (LR) solution infused by gravity, LR under pressure (300 mmHg), blood (350 ml packed RBCs + 50 ml NS) infused by gravity and blood under pressure were performed with each warmer. Infusion apparatus consisted of: fluid bag => drip chamber tubing => stopcock => warming cartridge => extension tubing => thermistor => IV catheter. Ambient, warmer, fluid and outlet (Tø) temperatures (°C) and infusion time (sec) were recorded.

Results: Average infusate temperature was 20.9 °C for crystalloid and 6.7 °C for blood. The flow rate (Flow) and a heat transfer coefficient (Hc) were calculated as follows:

$Hc = \Delta T_1 \cdot Flow \cdot \Delta T_2^{-1}$ $(ml \cdot min^{-1})$

$Flow = 60 \cdot Volume \cdot Time^{-1}$ $(ml \cdot min^{-1})$

$\Delta T_1 = Tø - T_{fluid}$ (°C)

$\Delta T_2 = T_{warmer} - 0.5 \cdot \Delta T_1$ (°C)

Crystalloid	**Gravity**				**Pressure**			
Warmer	Tø	Time	Flow	Hc	Tø	Time	Flow	Hc
Gorman-Rupp	33.53	773	78	30	31.63	277	216	60
Dupaco	33.47	1271	47	18	29.70	358	167	41
Travenol	34.23	724	83	33	31.77	262	229	70
Datachem	25.93	939	64	8	19.07	388	155	24
Level-1	35.70	783	77	36	32.40	256	234	79

Blood	**Gravity**				**Pressure**			
Warmer	Tø	Time	Flow	Hc	Tø	Time	Flow	Hc
Gorman-Rupp	30.70	1251	19	19	31.80	203	118	112
Dupaco	30.23	1790	13	13	32.47	371	65	58
Travenol	31.57	1063	23	23	32.87	218	110	132
Datachem	23.13	709	34	22	16.47	288	83	27
Level-1	32.57	724	33	33	33.07	134	179	168

Discussion: Fluid warmer performance can be assessed by determining heat transfer capacity using common clinical flow rates and fluids. Therefore, performance was assessed using Tø, Flow and Hc. A Tø approaching body temperature is desirable. Warmer performance in this regard was Level-1 > Travenol > Gorman-Rupp > Dupaco > Datachem. The Datachem Tø was considered inadequate. Flow depended upon the simulation scenario, but we deemed it most important for pressurized fluid. Thus, flow performance was Level-1 > (Travenol & Gorman-Rupp) > (Dupaco & Datachem). Hc is useful for comparing overall thermal performance[1]. In this respect, performance was Level-1 > Travenol > Gorman-Rupp > Dupaco > Datachem. In conclusion, we felt the Datachem was inadequate for all situations simulated, the Dupaco was inadequate for pressurized infusions. Overall performance of the others was Level-1 > Travenol > Gorman-Rupp. Performance was inferior to previous reports for all units[2-5], but this is likely due to our model. Elimination of the extension tubing would undoubtedly improve warmer performance, but would make practical use of the IV line more difficult.

References

1. Hill: Physics applied to Anaesthesia. Boston: Butterworth, 1980:292-293.
2. Health Devices, 13(9):191-216, 1984 Jul.
3. Anaesthesia, 45:960-963, 1990.
4. Anesthesiology, 73(1):173-176, 1990 Jul.
5. Anesthesiology, 65(3A):A126, 1986 Sep.

S145

Title: EFFECT OF 6 *vs* 12 ml·kg^{-1} INTRAOPERATIVE TIDAL VOLUME ON POSTOPERATIVE PULMONARY FUNCTION: A PROSPECTIVE, CONTROLLED, BLINDED, RANDOMIZED STUDY

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Affiliation: Naval Hospital, Portsmouth, Virginia (Approved, sponsored and supported by the Bureau of Medicine and Surgery Clinical Investigation Program CID No. P-91-L-H00000-015:A)

Introduction: Conventional teaching indicates a tidal volume (VT) of ≥ 10 ml·kg^{-1} for intraoperative controlled ventilation (CV)[1]. However, a smaller VT (< 10 ml·kg^{-1}) is necessary for some surgical procedures (e.g. ESWL[2]). We studied two groups of patients to determine the influence of delivered VT on postoperative pulmonary function.

Methods: Twenty-nine ASA I and II nonsmoking adults without known lung disease undergoing elective, peripheral surgery in the supine position were studied. Standardized general anesthesia (GA) was administered with VT randomly set to either 6 (Group A) or 12 (Group B) ml·kg^{-1}. FiO_2 and respiratory rate were varied to keep SaO_2 ≥ 94% and $ETCO_2$ at 35 mmHg while all other ventilatory parameters were held constant. Pulmonary function testing (PFT) (Forced Expiratory Volume in 1 second [L], Forced Vital Capacity [L], FEV1/FVC [%] [Ratio], Peak Flow [L·sec^{-1}] and Forced Expiratory Flow from 25-75% of FVC [L·sec^{-1}]) was done preoperatively (PRE), prior to discharge from the postanesthesia care unit (PACU) and on the morning after surgery (POD1) using a portable spirometer (L.A.P. Spirometer, Timeter Instrument Corporation, St. Louis, MO). Multiple ANOVA was used to analyze group demographics and differences in PFT between the three data collection points by multivariate variance analysis with the student's t-test.

Results:

Group	No.	(yr) Age	M/F	(min) OR Time	(cm) Height	(kg) Weight	(ml·kg^{-1}) VT
A	16	28±9	15/1	133±48	180±8	82±11	6.4±1.5
B	13	23±3	13/0	126±42	178±10	84±13	11.8±1.0

	Group	FEV1	FVC	Ratio	PF	FEF
PFT	A	3.5±0.6	4.3±0.7	83±13	6.1±2.4	4.1±1.4
Values	B	3.2±0.8	3.8±1.0	85±11	5.3±2.5	3.5±1.1
	Group	ΔFEV1	ΔFVC	ΔRatio	ΔPF	ΔFEF
PACU	A	-0.52	-0.54	-0.81	-0.89	-0.69
vs	B	-0.38	-0.44	0.23	-0.28	-0.09
PRE	p value	0.64	0.81	0.83	0.44	0.19
POD1	A	0.08	0.04	-1.27	0.26	0.27
vs	B	0.23	0.39	-3.82	0.15	-0.11
PACU	p value	0.64	0.29	0.69	0.89	0.53
POD1	A	-0.48	0.54	-2.13	-0.64	-0.47
vs	B	-0.17	0.09	-3.36	-0.07	-0.21
PRE	p value	0.41	0.30	0.84	0.50	0.64

Discussion: Changes in pulmonary function during GA[3] can be reliably determined by PFT[4]. We found the expected decrements in pulmonary function following GA with CV with some improvement by the next day. However, the two groups were clinically and statistically similar in this regard (p = 0.19-0.90). We conclude that VT of 6 and 12 ml·kg^{-1} produce similar PFT changes and that GA may be safely administered using smaller VT provided $ETCO_2$ and SaO_2 are maintained.

References:
1. Miller, ed: Anesthesia. New York: Churchill Livingstone, 1990: 2178.
2. Anesthesiology, 1988; 68:272 276.
3. Critical Care Clinics 1987; 3(2):287-306.
4. Med Clin North Am 1987; 71:399-412.

S146

TITLE: COMPARATIVE NEUROMUSCULAR EFFECTS OF VECURONIUM IN THE ADDUCTOR AND ABDUCTOR LARYNGEAL MUSCLES AND ADDUCTOR POLLICIS IN HUMANS

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The wide range of sensitivities to neuromuscular blockade has been reported between different muscles[1]. The present study was undertaken to compare the sensitivity of the adductor and abductor muscle of vocal folds, and the adductor pollicis muscle to vecuronium in humans.

METHODS: The protocol was approved by the Ethics Committee. Five ASA 1 and 2 patients (4 male, 1 female), weighing 53 to 66 kg, scheduled for resection of the larynx, were anesthetized with thiamylal 4mg/kg and fentanyl 3-5ug/kg. The trachea was intubated with the aid of SCC 1mg/kg. Mechanical ventilation was instituted, and anesthesia was maintained with fentanyl-nitrous oxide-oxygen. No volatile agents was given. After the skin, subcutaneous tissue and infrahyoid muscles were carefully separated and retracted to obtain access to larynx, the recording wire electrodes were inserted into the posterior cricoarytenoid (PCA, abductor) and the cricothyroid (CT, adductor) muscles under direct view. The evoked electromyographical responses of the PCA and CT muscles were quantified simultaneously in an identical manner by supramaximally stimulating the recurrent and the superior laryngeal nerves at 0.1 Hz and 0.2 msec. The ulnar nerve was stimulated and the force of the adductor pollicis (AP) muscles was also measured. Vecuronium was continuously infused at rate of 0.01 mg/kg/min.

RESULTS: Vecuronium produced neuromuscular blockade more rapidly on the AP than on the CT and the PCA. In comparing the CT and PCA, onset time was longer at the PCA than at the CT(figure).

DISCUSSION: Ideal intubation conditions dependent on adequate relaxation of respiratory and upper airway muscles. The findings of this study confirmed the difference in sensitivity of laryngeal muscles and peripheral muscles. We also found that the CT was more sensitive to vecuronium than the PCA.

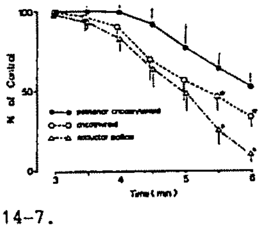

Figure. The time courses of twitch responses at three muscles after vecuronium. Data are mean £S.D.
☆ p<0.05 compared with PCA
* p<0.05 compared with CT

References
1. Anesthesiology 1983;58:414-7.

S147

Title: THE EFFECT OF DESMOPRESSIN ACETATE ON BLOOD PRESSURE IN RATS: WHAT IS THE MECHANISM?

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Desmopressin acetate (DDAVP) is known to cause hypotension in humans.[1] Clinical studies have revealed that the hypotension is caused by a decreased systemic vascular resistance (SVR) when DDAVP is rapidly administered (over either 5 sec or 5 min), and that it is not caused by histamine release.[2] A laboratory report concluded that DDAVP is a potent relaxant of vascular aortic rings of rat and rabbit.[3] Since the aorta is not a resistance vessel, this observation may not be clinically relevant. Our study evaluated the vasodilatory effects of DDAVP on isolated hindquarter vascular bed in live rats, and assessed the response after pretreatment with blockers.

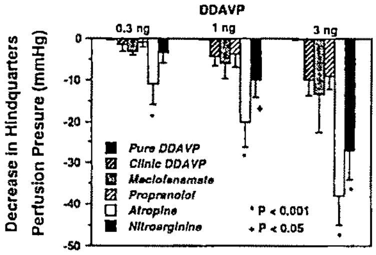
METHODS: With ACAR approval, 20 Sprague Dawley rats (400-500 g) were anesthetized with intraperitoneal pentobarbital anesthesia (50 $mg \cdot kg^{-1}$). The carotid artery, EJV and abdominal aorta were cannulated by cutdown; mean arterial pressure (MAP) and hindquarter perfusion pressure (HPP) were recorded. Rats were placed into 4 groups (5 each); each rat serving as its own control. Each group received a clinical preparation of DDAVP (Rorer) and a pure laboratory preparation of DDAVP in doses of 0.3-3 ng. Group I tested the DDAVPs before and after meclofenamate (M)(1.5 $mg \cdot kg^{-1}$), a cyclo-oxygenase inhibitor; Group II, before and after propranolol (P)(0.5 $mg \cdot kg^{-1}$), a beta adrenergic receptor antagonist; Group III, before and after atropine (A)(1 $mg \cdot kg^{-1}$), a muscarinic receptor blocker, and Group IV, before and after nitroarginine (N)(5 $mg \cdot kg^{-1}$), an inhibitor of nitric oxide synthesis. Chlorobutanol (C)(25-75ug), the preservative in clinical DDAVP, was tested for changes in HPP. Variables measured for each group were MAP and pre and maximal change in HPP; data was compared using t-Test ($p \leq 0.5$ is significant).

RESULTS: MAP remained constant throughout. HPP decreased with increasing doses of clinical DDAVP as compared to saline controls ($p<0.05$)(Table), while no change in HPP occurred with pure DDAVP. There were no changes after M or P blockers with either DDAVP, however an increase in HPP with both A and N was noted ($p<0.001$). C caused no effect in HPP.

DISCUSSION: Clinical studies have shown a decrease in MAP associated with a fall in SVR.[1,2] Clinical DDAVP causes significant dose dependent vasodilation of the hindquarter vascular bed of the live rat. There appears to be no effect from blockade of b-adrenergic or arachidonic acid product receptors. Atropine and nitroarginine may augment the vasodilation, suggesting either direct or receptor activity. The preservative of clinical DDAVP appears to have no vasodilatory effect. V1 and V2 antagonists are being tested with DDAVP to determine direct receptor effects.

REFERENCES:

1. Anesthesiology 71(3A):A488, 1989
2. J Cardiothorac Vasc Anesth 5:139-141,1991
3. Anesthesiology 72:858-864, 1990



S148

Title: DOES KETOROLAC, A NEW ANALGESIC, DECREASE POST-OPERATIVE NARCOTIC REQUIREMENTS, NAUSEA/VOMITING, AND UNSCHEDULED HOSPITAL ADMISSIONS: A RETROSPECTIVE ANALYSIS

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Ketorolac tromethamine (Toradol^R) is a recently FDA approved, intramuscular nonsteroidal anti-inflamatory analgesic.[1] It has been shown to have a narcotic sparing effect,[1,2] as well as lack of cardiorespiratory depression.[3] This study retrospectively evaluated patients receiving ketorolac for postoperative analgesia as compared to narcotics in terms of narcotic requirements, postoperative anesthesia recovery (PAR) and outpatient (OP) time, number of unscheduled admissions for outpatients, and incidence of nausea/vomiting.

METHODS: After IRB approval, ninety-eight patients' charts were reviewed. Fourty-nine subjects who received ketorolac postoperatively, as soon as entering the PAR, were matched with fourty-nine patients who had similar surgical procedures (operated on during the same six months) who did not receive ketorolac (Groups 1&2). Variables recorded were type and duration of procedure, patient age, gender, PAR and OP time (if patients were OP's), unscheduled admissions for OP's, ketorolac dose, narcotic requirements and doses, and nausea/vomiting. Data were also collected for Groups 3&4: OP's who received ketorolac; OP's who did not. Data for each of the two groups were compared by t-Test; p for statistical significance was set at 0.05.

RESULTS: Groups 1&2 did not differ in duration of surgery, patient age or gender; patients were matched for procedure, which ranged from D&C's to major spinal surgeries. PAR times for Groups 1&2 did not differ. PAR and OP discharges were based on patient discharge readiness, and not availablility of escort, transportation, etc. Group 3 had 22 patients, 21 in Group 4. The OP groups did not differ in duration of surgery, patient age, gender, or type of procedure. PAR and OP times for OP's did not differ. There was 1 unscheduled admissions for OP's in Group 3 and 0 for Group 4. Median and range of ketorlac dose for Group 1&3 was 60 mg (30-60). Narcotic requirements were not decreased for Group 1 compared to 2, or Group 3 compared to 4. Nausea/vomiting was not decreased between group 1&2, and 3&4.

DISCUSSION: Ketorolac is available for intramuscular injection for postoperative analgesia. It does not appear useful for both in- and outpatients in various procedures. It does not appear to shorten PAR and OP times and did not cause fewer unsheduled admissions for OP's. Narcotic requirements and nausea/vomiting do not appear decreased. Prospective studies are needed to confirm or reject these data.

REFERENCES: 1. Anaesthesia 1987; 42(7):727-31.
2. Anaesthesia 1990 45(7): 538-42.
3. Brit J Anaesth 1989; 63(5):601-34.

S149

ELECTRICAL ACTIVITY DURING CARDIOPULMONARY BYPASS IS ASSOCIATED WITH MYOCARDIAL INFARCTION

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INTRODUCTION: Ischemia during cardiopulmonary bypass (CPB) may be associated with perioperative myocardial infarction (MI). The aim of this study was to determine if the determinants of ischemia such as the durations of CPB, aortic occlusion (AO), and the low amplitude cardiac electrical activity recorded on the body surface during cardioplegic arrest, are associated with perioperative MI in patients undergoing coronary artery bypass surgery (CABG).

METHODS: After Institutional Review Board approval, informed consent was obtained from 120 patients, 15 of whom were undergoing reoperation. In 84 of these patients, Marquette 8500^R 3 channel amplitude modulated Holter monitor was used to record modified leads CM_6, III and I during CPB. The tapes were analyzed by Marquette 8000^R Laser Holter System to determine the period of low amplitude cardiac electrical activity during cardioplegic arrest. Care was taken to avoid the effect of artifacts. MI was defined as CK-MB≥25 IU/L within two days after surgery. The duration of CPB and AO were determined for all patients.

RESULTS: Eighteen patients, eight of whom were having reoperation had MI. One of them required an orthotopic heart transplant and is not included in further analysis. As shown in Table 1, the duration of CPB and AO were related to the group type (P<0.001). (n=number of patients).

Table 1: Duration of CPB and AO

Duration (minutes)	First Operation		Reoperation	
	Non-MI	MI	NON-MI	MI
	n=95	n=10	n=7	n=7
CPB	87±29	85±19	113±31	143±44
AO	49±20	53±11	63±15	78±14

Thirteen of the patients with Holter monitoring had MI. For patients with and without MI, Table 2 presents (A) the period of electrical activity during cardioplegic arrest and, (B) the percentage of the total period of cardioplegic arrest during which low amplitude cardiac electrical activity was present. The values are significantly higher for the MI groups.

Table 2: Association of low amplitude electrical activity with MI.

Variable	Non-MI	All MI	
	(n=71)	(n=13)	
(A) (Minutes)	13±19	34±26	P<.001
(B) (%)	26±35	56±42	P<.009

DISCUSSION: It has previously been shown that the low amplitude cardiac electrical activity recorded by right atrial electrodes is associated with perioperative MI[1]. In these patients, though the durations of CPB and AO were not associated with perioperative MI, the presence of ischemia during AO, as signified by low amplitude cardiac electrical activity recorded on the body surface, is associated with MI. The duration of such activity was unexpectedly high. When such activity is observed, steps may be taken to improve the myocardial protection. Alternative measures of ischemia during CPB, such as myocardial pH, have also been shown to correlate with MI. A possible reason for this is that ischemia may damage the coronary arteries[2] and make them susceptible to vasospasm and thrombosis.

REFERENCES: (1) Mullen JC, Khan N, Weisel RD, et al.: Atrial activity during cardioplegia and postoperative arrhythmias. J Thorac Cardiovasc Surg 34:558-565,1987
(2) Lindal S, Sorlie D, Jorgensen L: Endothelial cells of the cardiac microvasculature during and after cold cardiplegic ischemia. Comparison of endothelial and myocyte damage. Scand J Thor Cardiovasc Surg 22:257-265,1988

S150

IDENTIFICATION OF THE ONSET AND TRIGGERS OF MYOCARDIAL INFARCTION DURING CORONARY ARTERY BYPASS SURGERY

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INTRODUCTION: The aim of this study was to use electrocardiographic (ECG) monitoring to identify the time of onset and triggers of myocardial infarction (MI) during coronary artery bypass surgery.

METHODS: After Institutional Review Board approval, informed consent was obtained from 120 patients undergoing coronary artery bypass surgery, 15 of whom were undergoing reoperation. A modified 12-lead ECG was digitally recorded intraoperatively approximately every 3 minutes. Detailed information about hemodynamics, drugs administered and clinical activity was also recorded. Three lead Holter monitoring was performed from the evening prior to surgery and up to 48 hours after surgery.

Ischemia was defined as a new reversible 1 mm ST deviation. Myocardial injury leading to MI was defined as a new persistent 1 mm ST elevation in a lead with a predominantly positive QRS complex. ST elevation due to cooling, defibrillation, transient conduction changes on reperfusion after cardiopulmonary bypass, and pericarditis were ignored. Patients with CK-MB≥25 IU/L up to 2 days after surgery were considered to have MI.

RESULTS: Seven patients had new persistent ST elevation in the pre-bypass period. Two of these patients who needed grafts to the right posterior descending coronary artery, had persistent ST elevation and right ventricular dilation after pericardiotomy. The remaining five patients were undergoing reoperation. Three of them, who had unstable angina, had persistent ST elevation with increased heart rate caused by difficult tracheal intubation in one patient and pancuronium in two patients. One patient had a massive graft artheroembolus on the manipulation of an ectatic graft. One other patient had graft artheroembolus or thrombotic occlusion on manipulation of the heart.

Two patients did not have new intraoperative ST elevation and were considered to have MI during cardiopulmonary bypass. One patient emerged from bypass with a complete left bundle branch block and was considered to have MI because of inadequate cardioplegic protection. The second patient who was having reoperation was considered to have a graft atheroembolus during cardiopulmonary bypass.

Nine patients, two of whom were undergoing reoperation, developed persistent ST elevation in temporal association with the administration of protamine. The associated hemodynamic changes were small and did not show a trend. Five of these had a history of MI in the previous six months, three others had a history of MI. Three patients had prior MI and type I diabetes.

The patients with MI had a significantly longer duration of low amplitude cardiac electrical activity, recorded by the Holter monitor, during cardioplegic arrest.

The major risk factors for intraoperative MI and their respective odds ratios and p values were: reoperation (10.9,p<0.01) intraoperative pre-bypass ischemia (3.9,p<0.08), and history of MI (3.4,p<0.05). Three patients developed new Q waves in lateral leads and one of them in the inferior leads also. All patients recovered to be discharged from the hospital.

DISCUSSION: Thus the MIs in patients undergoing the first operation may occur primarily because of the damaging effect on the coronary endothelium of atherosclerosis, ischemia, cordioplegia and reperfusion; which predispose to the occurrence of vasospasm and thrombosis on the administration of protamine; especially in the presence of diabetes or a preexisting thrombus due to a prior MI. The increased incidence of MIs in patients undergoing reoperation may primarily be because of thrombosis or atheroembolization of old grafts prior to revascularization.

S151

Title: Clonidine and total intravenous anesthesia during intracranial surgery
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Hemodynamic stability and rapid emergence are essential for anesthesia during intracranial surgery. In this respect we examined the effects of clonidine vs. placebo in total i.v. anesthesia.

Methods. After institutional approval 20 consenting patients undergoing craniotomy for a brain tumor entered the study. Induction was with propofol (P) 2 mg/kg, fentanyl (F) 10 mcg/kg and vecuronium. After intubation and randomisation 10 patients received clonidine 300 mcg i.v.(C-group) and 10 patients received saline as placebo (Pl-group), according to a double blind protocol. Maintenance was with P infusion 0.17 -0.1 mg/kg/min , F infusion 0.033 mcg/kg/min until 60 min before the end of P infusion, and vecuronium. Ventilation was with oxygen in air. If mean arterial pressure (MAP) rose 20 % above baseline F 200 mcg was given, and labetalol was added if MAP remained high. After eye opening 3 psychomotoric function tests were performed (I day and date,II countdown,III naming coins between the fingers when blinded) till pre-op. values were reached.Data were analysed with Students-t-test and Wilcoxons two sample test.

Results: In the Pl-group 15 top-up doses F were given compared with 2 in the C-group. In the Pl-group 8 patients needed labetalol compared with 2 in the C-group. The table shows the values of MAP. In the C-group MAP remained stable throughout the procedure in contrast to the Pl-group. After the end of anesthesia, eye opening times 23.9 vs 15.2 minutes in the C-group resp. Pl-group, and performance test I (45.9 vs 21.1 min) and test II (43.8 vs 24.1 min) were not significantly different. Test III was significantly longer in the C-group compared with the Pl-group (52.1 vs 29.5 min). Post-op. hypertension defined as BP above 160-90 mm Hg was seen in one patient in each group.

Table: MAP mmHG (mean ±SD)

	Clonidine group (n=10)	Placebo group (n=10)
baseline	97.0±7.1	94.5±6.0
post induction	66.7±12.8**	70.6±14.0**
placing head pins	89.4±17.9	108.0±11.1**#
before incision	72.2±14.4**	87.6±11.9#
post incision	78.6±15.4**	103.3±11.0*##
opening dura	81.5±12.0**	93.8±11.9#
cessation fentanyl	71.5±11.6**	76.0±6.8**
cessation propofol	80.4±21.3*	80.2±12.0**

* P<0.05, **P<0.01, differences within the group compared to preinduction value; # P<0.05 and ## P<0.01, intergroup differences

Conclusion: Clonidine treated patients have greater hemodynamic stability than patients in the placebo group during total i.v. anesthesia for brain surgery, but recovery time is longer.

S152

Title: **A PORCINE MODEL FOR DIRECT AND CONTINUOUS IOP MEASUREMENT**

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Introduction: Control of intraocular pressure (IOP) is a concern in ophthalmic anesthesia [1]. Assessment of the IOP effects of positioning, ventilatory modes and drugs is ideally performed by direct anterior chamber manometry. The invasiveness of such monitoring, however, restricts its application to the experimental setting. Rabbits, cats and monkeys should not be used, because paracentesis breaks down the blood aqueous barrier [2, 3, 4]. As a consequence of animal protection legislation and public opinion, the experimental use of animals is shifting away from the classical models (cats, dogs, primates) towards food animals. In the U.S., the dog model is increasingly replaced by the pig [5], in Europe, preferential use of the pig model for experimental research was recently suggested by a working group of the *European Academy of Anaesthesiology* [6]. A survey of porcine experimental models presented at the 1990 ASA meeting revealed that 25 kg appears to be the body weight, preferred by experimental anesthesiologists. Though pigs have been used successfully for IOP studies [7], normal values for anesthetized and ventilated pigs have not been reported.

Methods: With approval by the state animal protection committee, we have performed cannulation of the anterior chamber in 60 piglets (German landrace, 9±1 weeks, mean weight 25.5 kg), using a heparin coated 22 G teflon cannula. Pigs were anesthetized (piritramide 2.25 mg/kg*h, pancuronium 0.4 mg/kg*h, F_iN_2O 0.6), normoventilated (et$[CO_2]_x$ 4.7%), normovolemic ($PCWP_x$ 6.0 mmHg / CVP_x 6.0 mmHg), and normothermic (T_x 39.8°C). IOP^x readings were recorded after stabilization, but not earlier than 1 hour after cannulation. Six hours later, aqueous humor was sampled from *both* eyes, and analyzed for protein content (parameter of blood-aqueous-barrier integrity).

Results: Under defined conditions, and with the zero reference point at the level of the porus acusticus externus, mean IOP ± SD was 12.4 ± 3.3 mmHg, $\tilde{x} = 12$, range = 7-19, 95 %-confidence interval = 10.6-13.7 mmHg. Mean protein concentration in the aqueous of the cannulated eyes was not significantly different from the concentration in control eyes.

Discussion: The pig is a promising model for experimental ophthalmic anesthesia. IOP may be monitored by direct manometry, which also allows for deliberate IOP modification and measurement of elastance. Anterior chamber cannulation is easily accomplished and does not compromise blood-aqueous-barrier integrity in pigs. Mean IOP in anesthetized landrace pigs of 25 kg body weight is 12 mmHg.

REFERENCES:

[1] Anaesthesist 37:458, 1988. [2] Invest Ophthalmol Vis Sci 18:361, 1979. [3] Exp Eye Res 32:635, 1981. [4] Invest Ophthalmol Vis Sci 18:1050, 1979 [5] Lab Animal Sci 34:383, 1984. [6] Eur J Anaesthesiol 5:287, 1988. [7] Br J Ophthalmol 58:514, 1974.

S153

TITLE: TIME AVERAGED SIGNAL ANALYSIS IN CENTRAL VENOUS PRESSURE MONITORING

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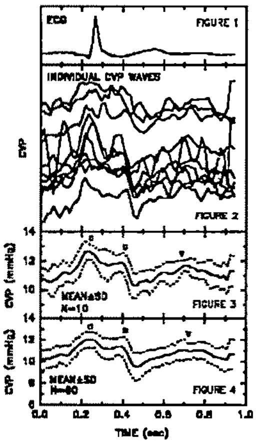
Introduction: The waveform of the central venous pressure (CVP) pulse has long been recognized to contain much information that is of value in cardiac diagnosis.[1] The most notable components include the amplitudes of the a, c, and v waves and the slopes of the x and y descents. Clinicians monitoring the CVP, however, mostly view the CVP as primarily a mean pressure measurement due to difficulty in detecting the various components of the waveform out of the "noisy" signal. It is also difficult to correlate the components with the P and R waves of the ECG while the waves are moving and are a considerable distance apart on most patient monitors. This study looked at the application of time-averaged signal analysis of CVP waveforms gated to the ECG R wave in the hope of providing a stable noise free waveform which could be easily interpreted.

Methods: This study was exempted from Institutional Review Board approval as it utilized only data from a previously developed library of ECG and CVP signals recorded on a frequency modulated analog tape recorder (Vetter model B). These signals were originally derived from patients undergoing cardiac surgical procedures via the CVP port of a pulmonary artery catheter (Abbott 41233-01) from the analog output of the patient monitor (Spacelabs 90305). The analog tape recordings were digitized via an analog to digital convertor (Data Translation DT-2801A) operating in a PC-AT computer running ASYST (Macmillan Software). The digital sampling rate was 64 Hz. After digitization the waveforms were time averaged.

Results: Ten unprocessed waveforms synchronized to the ECG (fig 1) are demonstrated in fig 2. Note the difficulty in discriminating the a, c, and v waves on most individual traces. After time averaging 10 beats (fig 3) the individual waveform components become easily discernible. Additional time averaging totalling 60 beats (fig 4) further improves signal to noise ratio.



Discussion: Signal averaging techniques result in an improved signal to noise ratio since noise which is unrelated to the ECG and cardiac cycle will be reduced in the process. Obtaining noise free waveforms would allow continuous trending of the a, c, and v waves and x and y descent slopes.

Conclusion: Signal averaging techniques provide an excellent method of processing CVP information aiding clinical diagnosis based on waveform analysis.

References: 1. Mark JB: Central venous pressure monitoring: Clinical insights beyond the numbers. J Cardiothorac Anesth 5(2):163-173, 1991.

S154

Title: INCIDENCE AND RISK FACTORS OF SUPRAVENTRICULAR TACHYARRHYTHMIAS DURING TOTAL JOINT ARTHROPLASTY

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Perioperative supraventricular tachyarrhythmias(AF/SVT) have been long recognized as a complication following major surgery, but little is known about the incidence following major non-thoracic surgery. We prospectively studied 1210 patients undergoing total hip or knee arthroplasty to determine the incidence of AF/SVT, and to identify variables that would influence this incidence.

All patients in sinus rhythm preoperatively having a total hip or knee arthroplasty between May 1 and December 31, 1990 comprised the study population. 96.6% of patients received an epidural anesthetic with either bupivacaine 0.75% or lidocaine 2% plus epinephrine 1:200,000 or 1:300,000; 2.8% had general anesthesia and 0.6% had spinal anesthesia. Medications consisted of midazolam and/or fentanyl sedation in those given regional anesthetics; and sodium pentothal, N2O, fentanyl, midazolam, vecuronium, and isoflurane in those given general anesthesia. Dosages were determined by the anesthesiologist as clinically indicated.

A 12 lead electocardiogram (EKG) was obtained in all patients during the week preceding surgery. Continuous EKG monitoring was begun on arrival in the operating room, and continued for at least 3 hours postoperatively. Whenever AF/SVT was suspected because of the monitor display, symptoms or tachycardia, a standard 12 lead EKG was obtained. For the purposes of this study, it was exclusively those patients with a AF/SVT documented on a monitor rhythm strip or a 12 lead EKG that were considered to have had this arrhythmia.

Information on preoperative medical history and laboratory tests were collected on 583 patients, and analyzed using logistic regression and linear analysis to determine risk.

New onset AF/SVT was found in 38 patients, representing an incidence of 3.1%. Of these, 53% occurred intraoperatively, 8% in the PACU, 16% on post-operative day 1, 13% on post-operative day 2, 5% on post-operative day 3, and 5% on post-operative day 4. The only variables found to be independently associated with the perioperative development of AF/SVT were a history of atrial fibrillation, increasing age, left anterior hemi-block and atrial premature depolarizations on the preop EKG. There was no AF/SVT seen in those patients less than 50 years old that had none of the 3 other risk factors. Conversely, in those 60 or older with one or more positive risk factors(13% of the study population), the incidence was 18.2%. No statistical model was useful in predicting AF/SVT, partially because of the relatively low incidence in this population.

Thus, AF/SVT occurred relatively frequently in a large subgroup of patients undergoing major joint arthroplasty, which may have implicatons concerning prophylaxis and surveillance.

S155

Title: INCONSISTENT RELATIONSHIP BETWEEN AXILLARY AND TYMPANIC TEMPERATURE FOLLOWING GENERAL ANESTHESIA

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Introduction: Following general anesthesia (GA), body temperature (T) is routinely measured and recorded, upon arrival in the post anesthesia care unit (PACU). Prompted by the fact that axillary (Ax) T is known to vary with cutaneous blood flow, and our observation of the lack of a consistent relationship between intra-operative core T (naso-pharyngeal) and Ax T measured in our PACU, we prospectively compared Ax T and tympanic (Tymp) T in 560 consecutive patients admitted to the PACU.

Methods: Adult patients, having GA for at least 30 min. were studied. Upon arrival in the PACU, age, gender, ASA status, operation, operating room (OR) time and T, length of PACU stay (LOS), and Ax and Tymp T were recorded. Descriptive statistics, linear regression between Ax T and Tymp T, Ax T and LOS, Tymp T and LOS, and a t-test to compare Ax and Tymp T were done.

Results: 560 consecutive adult patients (268 males, 292 females) were studied. Mean age was 35 years (SD 11, range 17-69); ASA status: I-281, II-252, III-25, IV-2; mean OR time (min) 143 (SD 69, range 30-480); mean LOS (min) 77 (SD 30, range 57-250).

Temp (^{0}C)	Mean±SD	Min	Max	Variance
Ax	34.7±0.94	31.1	37.8	0.88
Tymp	35.4±0.74	32.9	37.4	0.54

Regression: Ax T = 0.707 Tymp T + 9.69, $R^2 = 0.31$, $p = 0.0001$; Ax T with LOS, $R^2 = 0.01$, $p = 0.02$; Tymp T with LOS, $R^2 = 0.02$, $p = 0.001$. Using a t-test, Ax T had a lower mean and considerably more variability than Tymp T ($t = 15.31$, $p < 0.001$).

Discussion: Our relatively homogeneous population can be explained by the nature of the hospital. With a high number of observations and narrow range of absolute values being compared, Ax and Tymp T had the expected highly statistically significant correlation. Clinically, however, even 1 ^{0}C may represent a significant difference. More important, Ax T had an inconsistent and unpredictable relationship (greater variability) with Tymp T, and less correlation with time to meet standardized discharge criteria (LOS). On the basis of our data we **recommend** that Tymp T be measured in preference to Ax T whenever feasible.

S156

Title: MEASURING ARTERIAL HEMOGLOBIN SATURATION (SaO2) AFTER ANESTHESIA: TIME FOR A NEW POST ANESTHESIA RECOVERY SCORE?

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Introduction: Alderete and Kroulik first described a scoring system (PARS) for the post-anesthesia care unit (PACU) in 1970[1]. The American Society of Anesthesiologists has now mandated measurement of SaO2 in the immediate post-operative period[2], a practice already followed in many PACUs. Prompted by the above, and our perceived lack of usefulness of color in the original PACU score, we prospectively studied 560 patients comparing the use of SaO2 instead of color in the PARS (SaO2 PARS or SPARS).

Methods: Adult patients admitted to the PACU following general anesthesia were studied prospectively. All patients received 40% inspired oxygen on admission. Age, gender, ASA status, scored components of the original PACU score (activity, respiration, circulation, consciousness and color) and SaO2 were recorded immediately upon arrival in the PACU. A reliable SaO2 reading on a non-shivering patient (FiO2 0.4) was scored as: > 91% = 2; 85%-90% = 1; <85% = 0. The SPARS was calculated using the above, instead of color. Also recorded was the time to meet standardized discharge criteria (LOS, min). Descriptive statistics, simple regression of PARS with LOS, SPARS with LOS and PARS with SPARS are reported.

Results: 560 consecutive patients (268 males, 292 females) were studied. Mean age was 35 yrs (s.d. 11, range 17-69); ASA status: I-281, II-252, III-25, IV-2); mean LOS (77 (s.d. 30, range 57-250); SaO2: ≥ 95%, 476; 90-94% ,73; 85-89% 8; ≤ 85%, 3. Color was scored 2 in 559 patients and 1 in 1 patient.

	Mean±SD	Min	Max	R^2 with LOS (p value)
PARS	8.7±0.9	4	10	0.026 (<0.001)
SPARS	8.7±0.9	4	10	0.021 (<0.001)

PARS = 0.892·SPARS±0.99, $R^2 = 0.84$, $p = 0.0001$

Discussion: As might be expected, the two PACU scores are very similar. The patient population studied was relatively young and healthy. Though probably different from a majority of hospitals, this homogeneous population enables a compilation and comparison of the two scores, without any skewing. The SaO2 was affected by the added inspired oxygen, but since this is a standard of care immediately following general anesthesia, it would be inappropriate to measure SaO2 on room air. In **conclusion**, our data suggests that substituting color by a more meaningful and less subjective criteria (SaO2), is a valid, and desirable improvement in the PARS.

References:
1. Anesth Analg 1970; 49:924-933.
2. A.P.S.F. Newsletter 1991, Vol. 6; No. 1:6.

S157

TITLE: COMPARATIVE SYSTEMIC TOXICITY OF INTRAVENOUSLY INFUSED BUPIVACAINE (B), COCAINE (C), AND LIDOCAINE (L) IN PIGS
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AFFILIATION: Dept of Anesth, Vanderbilt Univ & Depts of Anaesth, Surg & Liver Research Center, Univ of Cape Town
INTRODUCTION: Both medical uses of C and B and illicit use of C are sometimes associated with life threatening complications. Our previous experiments in rats suggested that both bupivacaine and cocaine induced toxicity started with respiratory arrest. The aims of our present experiments are 1) to study and compare C-,L-,and B-induced systemic toxicity, and 2) to find a mechanism(s) for lethality from these local anesthetic drugs (LA), and 3) to investigate the contribution of respiratory system effects on the other systems. **METHODS:** 24 male pigs weighing about 26 kg were divided into 6 groups of 4 each. Under sodium thiopentol and N_2O anesthesia trachea was intubated, a carotid arterial cannula and a Swan-Ganz catheter were placed. Then, ½ the animals were allowed to breathe spontaneously (SV) and ½ were ventilated mechanically (MV). After obtaining stable state as judged by respiratory and cardiovascular parameters, pigs were infused with either iv C, B (both, .8 mg/kg/min), or L (3.2 mg/kg/min) until the time of cardiac arrest (CA). Respiratory, hemodynamic parameters, ABG, temp, and K^+ levels were monitored. The times of occurrence of respiratory arrest (RA) and CA in SV animals and CA in MV animals were noted. **RESULTS & CONCLUSIONS:** 1) RA is the primary cause of death in all SV pigs; 2) MV significantly delayed the time of occurrence of CA ($P<.05$); 3) Significant decreases in heart rate, mean pressure, and cardiac output and significant increases in systemic and pulmonary vascular resistances occurred in all animals ($P<0.05$); 4) Significant hyperkalemia occurred in all pigs. Life threatening hyperkalemia occurred only in animals that received C; 5) L,B, and C produced similar respiratory and cardiovascular systemic effects with continuous administration of iv toxic doses in this model. **Table 1:** RA and CA times with the infusion of B, C, and L. (Values= mean ± SEM)

Drug	SV RA, Min	 CA, Min	MV CA, Min
B	3.35 ± 0.21	6.33 ± 0.29 *	17.36 ± 1.50 **
L	5.45 ± 0.55	9.36 ± 0.16 *	20.35 ± 1.70 **
C	12.3 ± 1.18	14.1 ± 1.05 *	146.0 ± 37.0 **

* $=P<.05$ when compared to RA, ** $=P<.05$ when compared to CA of SV pigs

S158

TITLE: INHIBITION OF PSEUDOCHOLINESTERASE (PCHE) AND HEPATIC MICROSOMAL ENZYME ACTIVITY (HME) DO NOT POTENTIATE COCAINE INDUCED SYSTEMIC TOXICITY (CIT) IN PIGS
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AFFILIATION: Dept of Anesth, Vanderbilt Hosp, Nashville, TN and Depts of Anaeth, Surg, and Liver Research Center, Univ of Cape Town, South Africa
INTRODUCTION: Cocaine (C) is metabolized both by PCHE and HME. It has been postulated that a low or absent PCHE may potentiate CIT. We have recently demonstrated that inhibition of PCHE did not increase CIT in rats and that CIT always start with respiratory arrest (RA) and cardiac arrest (CA) follows RA. The aims of this study are 1) to determine whether C is more toxic to respiratory system or cardiovascular system, 2) to investigate the contribution of respiratory system effects on cardiovascular system, 3) to determine whether inhibition of PCHE has any influence on CIT, 4) to determine whether inhibition of HME has any influence on CIT, and 5) to measure catecholamine levels with the infusion of toxic doses of C. **METHODS:** 24 male pigs were randomly divided into 6 groups of 4 each. Group 1 and 4 pigs were pretreated with normal saline, group 2 and 5 pigs were pretreated with Iso-Ompa, a specific PCHE inhibitor, and group 3 and 6 pigs were pretreated with cimetidine, a HME inhibitor, all intramuscularly. Under barbiturate and N_2O anesthesia, a carotid arterial cannula and a Swan-Ganz catheter were inserted for hemodynamic monitoring. Groups 1, 2, and 3 pigs were then allowed to breathe spontaneously (SBG) and groups 4, 5, and 6 were mechanically ventilated (MVG). After obtaining stable state, pigs were infused iv, with C (0.8 mg/kg/min) until the time of CA. Respiratory and cardio-vascular parameters, and potassium levels were monitored. **RESULTS:** RA is the primary cause of death in spontaneously breathing pigs and that mechanical ventilation significantly delayed the occurrence of CA ($P<.05$). There were no significant increases in catecholamine levels from the control values. Significant increases in K^+ were seen in all pigs. **CONCLUSIONS:** 1) Pretreatment of pigs with either saline, Iso-Ompa, or cimetidine resulted in a similar cardiovascular and respiratory systemic effects & 2) Neither PCHE nor HME inhibition caused potentiation of CIT.

TABLE: Values = mean ± SEM

Group	SBG		MVG	P
	RA (min)	CA (min)	CA (min)	*, **
Saline	12.5±1.3	14.1±1.1*	146±37**	<.05
Iso-ompa	11.3±1.2	14.6±1.8*	140±31**	<.05
Cimetidine	13.5±1.1	17.6±0.5*	165±46**	<.05

* =RA vs CA in SBG (t-test); ** =CA vs CA in SBG & MVG (ANOVA)

S159

TITLE: PSEUDOCHOLINESTERASE (PCHE) INHIBITION ALTERS COCAINE (C), ECGONINE METHYLESTER (EM), AND BENZOYLECGONINE (BE) BLOOD LEVELS IN PIGS

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INTRODUCTION: Both illicit and medical uses of C have been associated with a number of toxic reactions. C is an ester type local anesthetic, and is metabolized by PCHE to give rise to EM. A low or absent PCHE activity is said to potentiate systemic toxic effects induced by C. We have recently demonstrated that inhibition of PCHE decreased fatality rate from acute C administration in rats. We postulated that alterations in the metabolic pattern may be responsible for this protection. Therefore we studied the effect of inhibition of PCHE on C metabolism. **METHODS:** 8 male pigs (2 groups of 4) weighing about 26 kg each were included in the study. Pigs were given 3 mg/kg of C iv, following im, pretreatment with either saline (G1) or a specific PCHE inhibitor (Iso-Ompa 1 mg/kg) (G2). Arterial blood was collected for PCHE activity and for C levels before and for C, EM and BE levels for 24 hrs after the administration of C. A colorimetric method and an HPLC method were used to determine PCHE activity and C, EM and BE levels, respectively.

RESULTS: Statistically significant but clinically insignificant increase in C levels were seen in G2 pigs ($P<.05$). BE levels were significantly higher and EM levels were lower in G2 pigs ($P<.05$). PCHE of G1 & 2 pigs were 422±46 and 58±2 IU, respectively ($P<.05$). **CONCLUSIONS:** 1) Inhibition of PCHE resulted in a significant decrease in EM levels. 2) An accelerated C's metabolism by an alternative route resulted in a significant increase in BE levels, a major metabolite of C.

Table: Mean C (μg/ml), EM & BE levels (ng/ml).

Time Min	C levels		EM levels		BE levels	
	G1	G2	G1	G2	G1	G2
5	1.0	1.0	157	0	57	67
10	0.9	0.9	190	38	67	142
15	0.8	0.8	183	76	79	195
30	0.5	0.5	163	38	97	215
45	0.3	0.4	154	0	104	212
60	0.2	0.3	39	0	96	196
120	0	0.1	0	0	63	163
180	0	0	0	0	43	72

S160

Title: Pharmacokinetics of Single Dose Propofol in Children

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The purpose of this study was to define the distribution kinetics of propofol in children and to use the kinetic data in the development of a physiologically based pharmacokinetic (PBPK) model for propofol in children. Twenty-one children, ASA I and II, were enrolled in the study; these subjects were divided by age into three groups of seven children each, as follows:

Group I: 3-5 Years
Group II: 6-8 Years
Group III: 9-11 Years.

Following a bolus dose of 3 mg/kg over 0.5 minutes, plasma propofol concentrations were determined at 1.5, 3, 5, 7, 9, 12, 15, 20, 30, 45, 60, 90, 120 and 150 minutes. The data were fit into a two-compartment model using EDFAST.(1) The mean (± SEM) values for $t_{\frac{1}{2}\alpha}$ and $t_{\frac{1}{2}\beta}$ were 3.80 ± 0.39 and 51.5 ± 6.9 minutes, respectively. The central volume of distribution was 0.78 ± 0.07 L/kg. These values are consistent with those that have previously been reported. Since the duration of blood sampling was short, complete distribution did not occur, and the elimination kinetics of propofol could not be separated from the distribution phase. Thus, the mean calculated clearance of 0.057 ± 0.002 L/min/kg includes distribution as well as organ clearance and is higher than what European Literature has reported in children where sampling has been done for 24 hours.(2) When analyzed according to the age of the child, none of the pharmacokinetic parameters were found to be age-dependent over the age ranges studied. PBPK models for propofol in children of various weights successfully predicted the experimental data collected following a single intravenous bolus dose of propofol.

1. J Pharm Sci, 76:93-100, 1987.
2. Br J Anaesth 63(6):667-70, 1989.

Table 1

	Weight (kg)	$t_{\frac{1}{2}\alpha}$ (minutes)	$t_{\frac{1}{2}\beta}$ (minutes)	V_c (L/kg)	CL (L/min/kg)
Group 1	18.0 ± 0.9	4.4 ± 0.9	42.8 ± 7.6	0.77 ± 0.34	0.055 ± 0.008
Group 2	23.8 ± 1.7	3.40 ± 0.71	63.0 ± 18.5	0.63 ± 0.28	0.058 ± 0.016
Group 3	36.5 ± 5.4	3.40 ± 0.45	48.7 ± 5.8	0.94 ± 0.22	0.058 ± 0.008
Overall		3.80 ± 0.39	51.5 ± 6.9	0.78 ± 0.07	0.057 ± 0.002

Values expressed are Mean ± SEM

S161

TITLE: ELECTROMECHANICAL EFFECTS OF PROPOFOL AND THIAMYLAL ON ISOLATED CARDIAC MUSCLES

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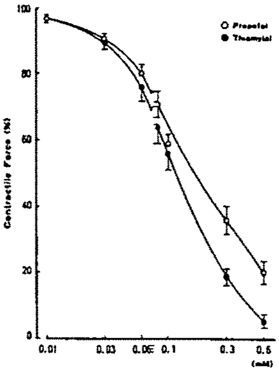
It has been reported that propofol exerts similar hemodynamic effects as thiopental. However, the direct electromechanical effects of propofol have not been evaluated. Then, we studied the electromechanical effects of propofol on isolated guinea pig papillary muscles and compared them with thiamylal.

The muscle preparations were superfused with the oxygenated Tyrode solution at 33 °C and were stimulated at a rate of 0.5Hz. Transmembrane potentials were recorded using conventional microelectrode techniques. Developed tension (DT) were simultaneously recorded.

Either propofol or thiamylal decreased DT in a dose-dependent fashion, but the depression by propofol was less than thiamylal (Fig. 1). The doses for 50% and 80% depression of DT were 0.2mM and 0.6mM for propofol, and 0.1mM and 0.3mM for thiamylal. Resting membrane potential (RMP) was not changed by propofol 0.2mM and 0.6mM, while it was significantly increased by thiamylal 0.1mM and 0.3mM (Fig. 2). Action potential amplitude (APA) was decreased by propofol 0.6mM and thiamylal 0.1mM and 0.3mM. Action potential duration (APD) was significantly shortened by propofol and thiamylal in a dose-dependent manner.

These results indicate that both propofol and thiamylal exert negative inotropism in isolated cardiac muscles and that this negative inotropism seems to be due to the decreased influx of extracellular Ca ion across the membrane. However, electromechanical behavior of propofol is different from that of thiamylal because changes in RMP and APA are different between propofol and thiamylal.



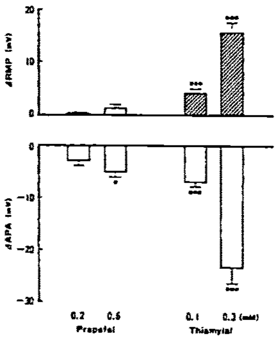


Fig. 1 (left): Dose-response curves of developed tension by either propofol or thiamylal.

Fig. 2 (right): Changes of RMP (the upper panel) and APA (the lower panel) by propofol and thiamylal.

S162

Title: Respiratory complications after alfentanil anesthesia in pediatric ambulatory surgery

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Introduction: Alfentanil, a rapid onset, short duration narcotic, is ideal for pediatric ambulatory surgery. However, narcotics are known to depress respiration. Thus, we evaluated the incidence of respiratory complications following alfentanil anesthesia.

Methods: With institutional approval and consent, 100 children (tonsillectomy n=75 and herniorrhaphy n=25) ages 3-12 years were studied. After an iv induction with thiopental, droperidol, atropine and vecuronium, alfentanil (100µg/kg) was infused over 1 minute. Post-intubation, anesthesia was maintained with 70% N_2O and supplemented with incremental doses of alfentanil (5-15µg/kg) up to 45 µg/kg for tonsils and 75 µg/kg for hernias if either the heart rate or systolic pressure were ≥20% above awake values. Isoflurane (0.5%) was added if these values persisted ≥20% above awake values. A regional block was administered to patients undergoing herniorrhaphy. After extubation, oxygen saturation (SaO_2) was monitored in transit to and in the recovery room. Respiratory complications were graded (I-III) according to the respiratory rate and intervention required. Data was analyzed (P<0.05) using Fisher's exact test and the unpaired t test.

Results: Respiratory complications occurred more frequently in children undergoing tonsillectomy compared to herniorrhaphy (Table). Complications did not correlate with the total dose or the time from the last dose of alfentanil to extubation. SaO_2 was ≤90% in 35% of children in transit to recovery.

Discussion: The greater incidence of respiratory complications after alfentanil for tonsillectomy may be attributed in part, to the nature of the surgery and to the larger dose of alfentanil. While alfentanil is effective for pediatric ambulatory surgery, respiratory complications occur more frequently after tonsillectomy than after herniorrhaphy.

Acknowledgement: Supported in part, with a grant from Janssen Pharmaceutica, Canada

TABLE

	Tonsillectomy	Herniorrhaphy
Age (yr)	5.5±2.2	5.1 ± 2.5
Wt (kg)	23±9.3	19.8±6.5
Anesth time (min)	27±6.5*	43.4±9.5
Dose (µg/kg)	135±11.4*	115±15.6
Dose (µg/kg/min)	5.9±1.4*	3.0±0.8
Last dose-extubation (min):		
Problems	12.6±4.7	34.0
No Problems	14.7±6.6	28.0±15.1

Data are means ± sd
* P<0.001 compared to herniorrhaphy

Post-operative respiratory complications:		
I (stimulation, RR<10)	6	1
II(jaw thrust, RR<8)	8**	0
III(CPAP/intubation)	6**	0

** P<0.02 grades II and III combined and compared to herniorrhaphy

S163

THE EFFECTS OF HALOTHANE and HYPERTHERMIA ON MASSETER MUSCLE RIGIDITY IN THE RAT. M.M. Keykhah, M.D., R.J. Storella, Ph.D., S. Begen, B.A. and H. Rosenberg, M.D., Dept. of Anesthesiology, Hahnemann University, Philadelphia, PA 19102

Introduction. It is now recognized that neuromuscular blocking doses of succinylcholine (SCh) produce a transient contracture of jaw muscles in many patients[1]. This masseter muscle rigidity occasionally causes difficulty in performing endotracheal intubation[1,2] and has been associated with susceptibility to malignant hyperthermia (MH)[3]. We examined the effect of halothane and hyperthermia on SCh-induced contractures of the jaw muscles in the rat.

Method. Male Wistar-Furth rats were anesthetized either with IP pentobarbital 50 $mg.kg^{-1}$ (**PEN**) or halothane 2% in O_2 (**HAL**). After tracheostomy for mechanical ventilation, the right femoral vessels were cannulated for blood pressure (**BP**), gases and pH monitoring, drugs and fluid infusion. The lower incisors were connected to a transducer for recording the isometric jaw muscles twitch tension (**TT**) in response to bilateral supramaximal mandibular nerve stimulation and the peak jaw muscles contracture (**PC**) induced by iv SCh injection. Rectal temperature was controlled by heat lamp with servo mechanism. In each group, the animals were assigned to a normothermic (37°C) and hyperthermic (41°C) subgroups and the peak contracture response to the iv injection of 0.75 $mg.kg^{-1}$ SCh was recorded at the desired temperature. Data were analyzed by analysis of variance and Duncan multiple range test and P<0.05 was considered significant.

Results. PC values after SCh injection was significantly higher in HAL 41°C subgroup than in other subgroups while TT was not different among subgroups (table 1). While there were differences between subgroups regarding some physiologic parameters (table 2), these disparities did not relate to the differences in the values of contracture.

Table 1 - PC and TT in grams.

	PEN		HAL	
	37°C (n=5)	41°C (n=5)	37°C (n=4)	41°C (n=5)
PC	1.7± 0.47	2.5± 0.41	2.1± 0.70	23.4±* 9.20
TT	167± 5.54	182± 16.85	185.5± 19.24	165.2± 4.36

Values are mean ± S.E.M.
*Significantly different from all the other Subgroups P<0.05

Table 2 - Physiologic parameters.

Groups	Subgroups	BP(mmHg)	PaO2(mmHg)	PaCO2(mmHg)	pH
PEN	I - 37°C (n = 5)	120± 8.9	397.2± 41.9	36.8± 0.9	7.37± 0.012
	II - 41°C (n = 5)	123± 6.2	357.6± 56.7	43.8±* 1.7	7.29±*♦ 0.033
HAL	III - 37°C (n = 4)	80±*‡ 0.0	314.0± 48.6	40.7± 3.17	7.37± 0.012
	IV - 41°C (n = 5)	61±*‡ 6.4	360.4± 30.7	46.2±* 2.13	7.29±*♦ 0.02

Values are mean ± S.E.M.
Significantly different from Subgroup I (*), II ( ) or III (♦) . P,0.05

Discussion. Our data indicate that halothane + hyperthermia enhance SCh-induced jaw muscles contracture. This enhancement is not readily explainable by changes in $PaCO_2$ and pH. Whatever the mechanism involved, it does not cause enhancement in twitch tension development. Although HAL or SCh may not initiate the muscle rigidity, the combined presence of these two factors exacerbate this muscle rigidity during malignant hyperthermia.

REFERENCES
1. Br. J. Anesth. 64:21-27, 1990
2. Anesth. Analg. 72:151-160, 1991
3. Can. J. Anesth. 37:31-15, 1990

S164

TITLE: COMPARISON OF ANESTHETIC DRUGS USED FOR SEDATION DURING CATARACT SURGERY

AUTHORS: M. Kimovec, M.D.(1), J. Bizzell, M.D., N. Caro, M.D., M. Patel, Ph.D.(2)
AFFILIATION: (1) Northwestern Univ. Dept. of Anes., Columbus Hospital, and (2) Univ. of Ill. at Chicago Research Resources C., Chicago, IL

The elderly patients coming for cataract surgery often express anxiety about the procedure and complain about pain during the retrobulbar block.[1] Many different techniques and drugs are used to sedate patients for the local block. We compared three common sedative regimens to evaluate their efficacy and to test the clinical impression that thiopental was superior over the other drugs used.

With institutional approval from Columbus Hospital IRB Committee and Northwestern University Human Subjects Committee and informed consent from the patients, forty-five available patients for cataract surgery were randomized into one of three groups. After noting the patient's anxiety level, each patient was given fentanyl 0.05 mg IV. Then one of three drugs was titrated to effect: fentanyl to a total 0.05 mg, thiopental to 100 mg, and midazolam to 2 mg. The anesthesiologist and surgeon were blinded as to which additional anesthetic was given and both judged the patient's level of sedation, self-control, and analgesia during the retrobulbar and facial block. During the block, a well-known melody, "London Bridge is Falling Down", was played with headphones into patient's ears. After surgery, the patients were questioned about recall of the block and song and acceptance of procedure. Complications were noted. Data was analyzed by ANOVA and Chi-square.

Patient demographics between groups were similar:

GROUP	M/F	AGE (yr)	WT (KG)	RECALL BLOCK	(Y/N) SONG
Fentanyl	5/10	71 ± 8	67 ± 13	6/9	9/6
Thiopental	5/10	69 ± 8	74 ± 19	6/9	8/7
Midazolam	3/12	72 ± 9	70 ± 12	3/12	4/11

Data in table is mean ± Standard Deviation.

After the fentanyl 0.05 mg, the average amount of drug given for sedation was an additional fentanyl 0.034 ± 0.011 mg, thiopental 53 ± 9 mg, or midazolam 1.3 ± 0.4 mg.

No statistical difference was noted in the sum of sedation, self-control, and analgesia scores, recall, of block or song, or patient acceptance. Complications noted included nausea (5 pts), vomiting (4), dizziness (3), snoring (2), sleepiness (1), anxiety (1), hypertension (16), oxygen desaturation < 94% (11), and arrythmia (1). Both the snorers were in the midazolam group.

Unexpectedly, no overall difference existed in sedation level, recall of the retrobulbar block or song, or patient acceptance using any of the three drugs, fentanyl, thiopental, or midazolam. This experimental design was unable to detect subtle differences between the three drugs.

REFERENCES:
1. JA McCarthy. Letter to the Editor. Ophthalmic Surgery 14: 607-608, 1983.

S165

Prolongation of Epidural Analgesia Using Bupivacaine in Glycerin Solution

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INTRODUCTION: Glycerin has long been used with phenol as a drug depot in control of intractable pain. However, through our literature review, glycerin has never been used to prolong the pharmacological effects of a local anesthetic, such as bupivacaine. Our study is an attempt to use the same mechanism to further extend the pharmacologic effects of a popular long lasting anesthetic in a commonly used technique.

PATIENTS AND METHODS: Following institutional approval and patient consent, 15 adult patients were entered into this study for relief of cancer pain. Patients were prospectively selected according to their primary lesions and problems, but their allocation to the study groups was random. Group I (n=8) received 5ml of 0.125% bupivacaine in normal saline epidurally via a previous implanted catheter. Later, when the pain returned to its original intensity, the same amount of the same strength anesthetic dissolved in 50% glycerin was given via the same catheter. Group II (n=7) received the both solutions, but in reverse order. The pharmacological effects were assessed by evaluation of the intensity and duration of sensory and motor blockade employing visual analogue scale and Modified Bromage Scale. Patients' vital signs were closely monitored during the study.

RESULTS: Our experimental experience revealed significant prolongation of analgesia with the glycerin solution as compared to the saline solution for both groups of patients (11.75 vs. 7.375 and 11.875 vs. 7.928 hrs, $P < 0.01$). The order of the solutions given did not have a statistical significance (11.75 vs. 11.875 and 7.375 vs. 7.928, $P > 0.05$).
Neither motor blockade nor other adverse effects/complications were observed in either group.

DISCUSSION: Modern clinical approach to the relief of chronic pain involves either modification of efferent nociceptive impulses or alteration of the central interpretation of those impulses. The former can be achieved by local application of either chemical (anesthetics, neurolytic etc) or mechanical (acupuncture, TENS etc) means. The later by parenteral medication. Nevertheless, when an organic cause exists, nerve blockade generally plays a major role in pain management. In addition to relief of chronic pain, this novel approach may have other clinical applications, such as relief of labor pain or postoperative pain.

S166

Title: HEATED BREATHING TUBES IMPROVE AIRWAY CLIMATE

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Introduction: Anesthesia ventilation with minimal fresh gas flow rates has been shown to improve climatization of respiratory gases [1]. Due to the influence of ambient temperature, however, optimal humidity [2] is achieved only after 120'. It was the aim of the present study to verify, whether optimization of inspiratory airway climate may be achieved earlier by means of heated breathing tubes.

Methods: A total of 26 prolonged anesthetics were conducted in adult patients using minimal fresh gas flow rates (FGF 0.6 L min^{-1}; AV1, Draeger, Lübeck, FRG) and silicon breathing tubes (length 1 m, I.D. 16 mm), containing a spiral heating wire (40 ohm, Ruesch, Waiblingen, FRG). Group I (n=10): control group, breathing tubes unheated. Group II (n=10): breathing tubes heated to 30° C (current generator: PE 1540 DC, 12 V, Philips, Belgium). Group III (n=6): breathing tubes heated to 36° C (18 V). Humidity and temperature were measured at the Y-piece, using a combined measuring device (Rotronic AG, Switzerland) [1].

Results: Inspiratory temperature in group II was significantly higher, as compared to control. In group III, both inspiratory temperature and absolute humidity were significantly higher, as compared to control; after 5' of ventilation, water content and temperature of inspiratory gases were significantly higher then in group I (fig. 1 and 2).

Discussion: The desirable airway climate [1, 2] is obtained with minimal fresh gas flow rates only after 120'. Thermostatically heated breathing tubes effectively reduce this delay.

Fig.1: Insp. temperature [FGF 0.6 L/min]
group III (heated breathing tubes) —●—
group I (control group) —□—

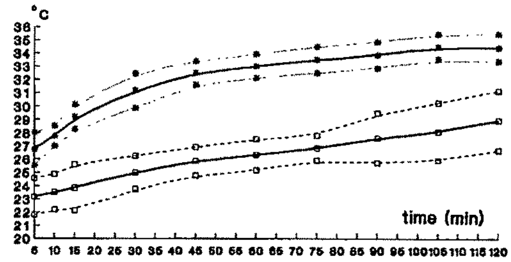
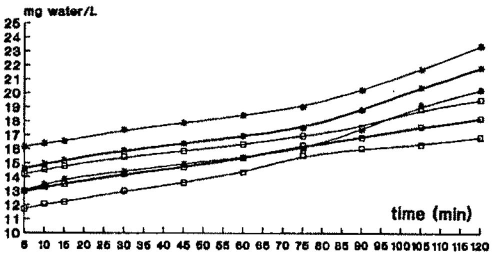


Fig.2: Insp. humidity [FGF 0.6 L/min]
group III (heated breathing tubes) —●—
group I (control group) —□—



[1] Acta Anaesth Belg 41:189 (1990). [2] Health Devices 12:155 (1983)

S167

TITLE: USE OF RECOMBINANT HUMAN ERYTHROPOIETIN IN A JEHOVAH'S WITNESS PATIENT

AUTHORS: H.M.Koenig, M.D., E.A.Levine, M.D., D.Resnick, M.D., W. Meyer,M.D.
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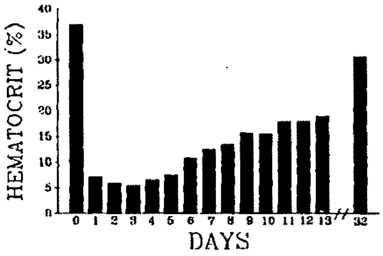
Introduction: Patients who bleed massively and refuse blood transfusions are at risk for morbidity secondary to the reduction in red cell mass and compromised oxygen carrying capacity. Erythropoietin (EPO), is a hormone normally produced by the kidney which stimulates erythropoiesis. Recombinant human erythropoietin (rHuEPO) is commonly used for patients anemia of chronic renal failure.[1] Accelerated recovery from acute postoperative anemia has been observed in rHuEPO treated primates.[2] We treated a severely anemic patient with rHuEPO when blood transfusion was not an option.
Materials/Methods: A 39 y/o Jehovah's Witness presented with in utero fetal demise and brisk vaginal bleeding at 28 weeks gestation. A diagnosis of placenta previa was made. Emergency cesarean section was performed under general anesthesia. Intravascular volume was maintained with crystalloids and hetastarch. Hematocrit (Hct) on admission was 37%. It reached a nadir of 5.6% on the first postoperative day. She was kept at rest, given oxygen, parenteral iron, and hyperalimentation. She was informed of the potential risks and benefits of r-Hu EPO, and with her consent, intravenous r-Hu EPO was initiated at 600 u/kg/day and was continued for 11 days. She responded with a brisk rise in Hct and a sustained elevation of reticulocyte count. No complications of the rHuEPO therapy were encountered. She was discharged home on vitamins and iron.

Results:



Discussion: Acceleration of erythropoiesis with rHu EPO has been demonstrated in acutely anemic patients who refuse transfusion.[3,4] Our patient was treated with a higher dose of rHuEPO than previously reported, and responded with a rapid rise in Hct. rHuEPO is safe, effective therapy for many patients with chronic anemia.[1,5] rHuEPO adjunct therapy should be considered for patients with acute anemia who refuse transfusion.
Conclusions: A severely anemic patient demonstrated a rapid rise in Hct and sustained elevation of reticulocyte count with rHuEPO therapy. rHuEPO adjunctive therapy may be indicated for severely anemic patients who refuse blood transfusions.

References:

1. NEJM 316:73-8, 1987.
2. J Trauma 29: 1134-1138, 1989.
3. J Trauma 30: 1406-1408, 1990.
4. Ann Int Med 112(7):552, 1990.
5. Lancet 2:1175-8, 1986.

S168

Title: Effect of diazepam and midazolam on heart rate variations

Authors: T.Komatsu, MD, T.Kimura, M.D., F.Sugiyama, M.D., M.Ito, M.D. and Y.Shimada, M.D.
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Introduction: Benzodiazepines have been advocated as preoperative medication to control fear and anxiety and to eliminate or suppress the stress reaction to anesthesia and operation. Their effect on autonomic cardiac reflex activity has been evaluated in many studies, but the equipment involved is difficult to use and too bulky for everyday use in the operating room[1]. Spectral analysis of heart rate variations offers noninvasive means to assess the activity of the autonomic nervous system in the operating room[2]. We compared oral diazepam, and intramuscular midazolam on the heart rate variations as an index of autonomic nervous activity.
Methods: After institutional approval and informed consent, 20 ASA I patients 18 - 42 years old scheduled for elective surgery were studied. They received either 10 mg of oral diazepam (Group 1) or 5 mg of intramuscular midazolam (Group 2) one hour before the surgery. Consecutive RR intervals were measured with an accuracy of 1 msec for 10 min on the preoperative day as control and 30 min after premedication in the operative room just before the induction of anesthesia. HR data were calculated every 0.5 sec (a total of 512 times) by the method of integral pulse frequency modulation, which used a low-pass digital filter with a cut off frequency of 0.5 Hz. Power spectral density of these data was computed using a fast Fourier transform. The areas of the spectral peaks within each measurement were calculated as follows: low-(LO, 0.04-0.09 Hz), mid- (MI, 0.09 - 0.15 Hz), and high-frequency areas (HI, 0.15-0.5 Hz). In considering the individual deviation in heart rate variations, we calculated the magnitude of each component area as percent of total power of the control of each patient. The mean ± SD was determined and was compared using analysis of variance.
Results: The results are shown in Table 1. None of the component area changed following diazepam as compared with control. On the contrary MI and HI decreased significantly following midazolam compared with control, while LO did not change.
Discussion: Our results showed significant reduction in MI and HI following midazolam, suggesting that midazolam interferes with both the sympathetic and parasympathetic components of autonomic nervous system. However, diazepam as premedication did not alter autonomic regulation of cardiovascular function. Since either intense activation or severe depression of autonomic nervous system can be dangerous in patient with ischemic heart disease and/or myocardial dysfunction in the preoperative period. Diazepam would be a better choice than midazolam as premedication.

References:

1.Br J Anaesth 56:725,1984
2.Anesthesiology 65:A139,1986

Table 1

	Group 1		Group 2	
	Control	Diazepam	Control	Midazolam
LO	30.1 ± 17.3	48.8 ± 33.5	51.1 ± 25.8	39.1 ± 25.4
MI	17.3 ± 7.7	22.9 ± 17.1	24.9 ± 21.5	6.4 ± 3.9*
HI	52.5 ± 21.9	51.2 ± 34.5	23.9 ± 24.9	8.0 ± 7.9*

Mean ± SD
* $P < 0.05$ vs Control

S169

TITLE: EFFECTS OF KETAMINE ON THE INTRACELLULAR Ca^{2+} TRANSIENT IN MAMMALIAN VENTRICULAR MYOCARDIUM

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Introduction. Ketamine exerts a negative inotropic effect after ß-adrenoceptor blockade or after myocardial norepinephrine depletion (1). The aim of this study is to investigate which mechanisms are involved in the negative inotropic effect of ketamine.
Methods. After institutional approval, five ferret right ventricular papillary muscles were microinjected with the Ca^{2+}-regulated photoprotein aequorin (2). Force (F) and aequorin luminescence (AL) were measured from isometric twitches before and after ketamine 10^{-6}M, 10^{-5}M, 10^{-4}M, and $3x10^{-4}$M in muscles pretreated with (±)-bupranolol 10^{-7}M. In four additional muscles peak AL was compared at equal F between control and ketamine 10^{-4}M + bupranolol 10^{-7}M + raised $[Ca^{2+}]_o$.
Results. After ß-adrenoceptor blockade, ketamine ≥ 10^{-4}M decreased both peak F and AL (Fig. 1). Peak AL did not differ at equal peak F before and in ketamine 10^{-4}M (Fig. 2).
Discussion. The intrinsic effect of ketamine to decrease myocardial contractility most likely results from a decrease in intracellular Ca^{2+} availability with no changes in myofibrillar Ca^{2+} sensitivity.
Supported by NIH GM 36365 and Mayo Foundation.

References 1. Cook et al., Anesthesiology 74: 880-888, 1991.
2. Blinks et al, Meth. Enzymol. 57: 292-328, 1978.

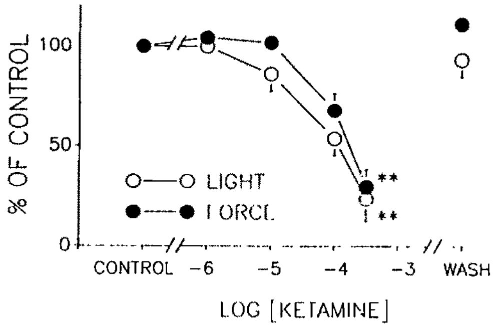

Figure 1. Effects of ketamine on peak AL and F in ferret ventricular papillary muscle (mean ± SD; n=5). **P < 0.01.

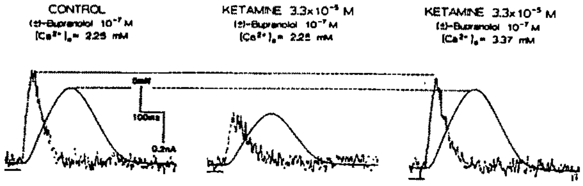

Figure 2. AL and F traces during isometric Ca^{2+} back titration experiment. 128 twitches were averaged in each panel.

S170

INFUSION OF GLUTATHIONE ENHANCES THE POST-ISCHEMIC FIBER-SHORTENING IN DOG HEARTS

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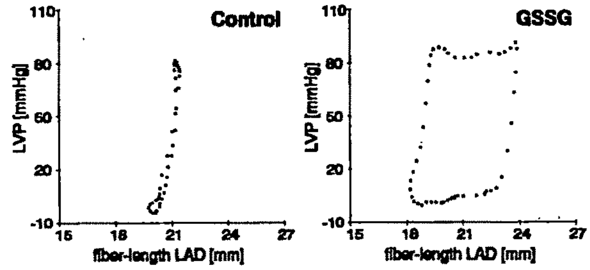
Introduction: Oxygen-free radicals are playing a crucial role during the recovery of myocardial function after reversible regional ischemia[1]. In submaximaly Ca^{++}-activated skinned cardiac fibers, Glutathione (GSH, 2-5 mM) has been shown to increase the contractile force[2]. The study presented here was designed to investigate the effects of glutathione (GSSG) in similar concentrations on the regional fiber-shortening of intact postischemic dog hearts.

Methods: In six anesthetized and mechanically ventilated beagles the descending branch of the left coronary artery (LAD) was ligated for 30 min. Ten minutes prior to the reopening the infusion of glutathione into the left atrium was started and continued throughout the experiment (GSSG-group). Animals assigned to the control group received identical volumes of Ringers solution. Myocardial fiber-length was measured by sonomicrometry, regional blood flow was estimated by injection of radioactive labeled microspheres.

Results: As depicted below (Pressure-length diagrams, obtained 10 min after onset of reperfusion), the GSSG-treated animals showed an improved myocardial segment-fiber-shortening during the reperfusion period as compared to controls.



Discussion: Glutathione seems to enhance the contractile status of the postischemic myocardium under conditions of oxidative stress. Further studies are required to prove, whether glutathione may have therapeutic relevance in patients during reperfusion after transient occlusion of coronary arteries.

References: [1] Basic Res. Cardiol. 84:591 (1989)
[2] Circulation 72:915 (1985)

S171

TITLE: LIDOCAINE SLOWS THE RECOVERY OF RESIDUAL NEUROMUSCULAR BLOCK INDUCED BY ATRACURIUM IN HUMAN

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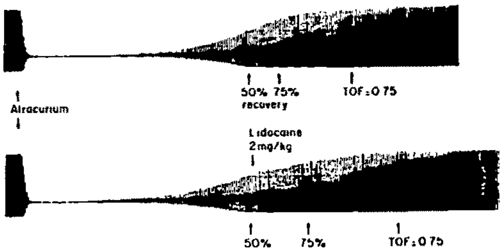
Intravenous lidocaine has been shown to slow the neuromuscular recovery induced by atracurium in cats(1). To smooth the emergence of anesthesia, lidocaine 1-2 mg/kg is often given iv at the end of surgery(2,3) when the patient may still has partial neuromuscular block. We studied the effect of lidocaine on the recovery of neuromuscular block induced by atracurium in human.

With institutional approval and informed consent, 30 ASA I or II patients, 18-49 y.o., 58-83 kg, undergoing elective orthopedic surgery were randomly divided into 3 groups of 10 each. Anesthesia was induced with thiopental and maintained with halothane (0.5% end-tidal) + 60% N2O + fentanyl. Trachea was intubated without the use of muscle relaxant, ventilation was controlled to maintain normocarbia. After intubation, the ulnar nerve was stimulated supramaximally at the wrist with train-of-four (TOF) mode every 12 seconds and the evoked compound EMG of the 1st interosseous muscle was recorded. After stabilization of the twitch responses, atracurium 0.2-0.25 mg/kg was administered iv to induce 95% of twitch depression. Neuromuscular block and recovery were recorded. Twenty minutes after the recovery of T1/T4 ratio>0.75, atracurium in the same dose was given. When the first twitch of TOF had returned to 50% of control, lidocaine 1, 1.5 or 2 mg/kg was given to patient in group A, B or C, respectively. Effect of lidocaine on the spontaneous recovery of neuromuscular block was quantified. Data were presented as mean ± SEM and analysed by Student's t-test. $p<0.05$ was considered significant.

Intravenous lidocaine siginficantly slowed the spontaneous recovery of neuromuscular block (from T1=50% to TOF ratio=0.75) induced by atracurium and it was dose-related (table)(figure). After iv lidocaine, arrhythmia was observed only in one patient in group C (transient bradycardia).

Since iv lidocaine 2mg/kg slows the neuromuscular recovery produced by atracurium (from T1=50% to TOF ratio=0.75) up to 1.5 times of control and might cause bradycardia, and iv lidocaine 1 mg/kg was effective in suppressing cough and bucking in the recovery period after general anesthesia(4); it may be unnecessary to use lidocaine 2mg/kg to smooth the emergence of anesthesia before extubation.

	Time(min) form T1=50% to TOF ratio=0.75		
Group	Without lidocaine	with lidocaine	P
A	14.2 ± 1.6	16.2 ± 1.9 *	< 0.025
B	16.6 ± 1.0	20.2 ± 1.2 *	< 0.005
C	15.2 ± 1.0	22.7 ± 1.6 *	< 0.005



REFERENCES:
1. Anesth Analg 68:S154, 1989. 2. Acta Anesth Scand 27:111-112, 1983. 3. Anesth Analg 57:506-507, 1978. 4. Anesthesiology 69:A635, 1988.

S172

Title: INTERACTION BETWEEN CARDIOVASCULAR AND ANESTHETIC DRUGS: APPLICATION TO AN EXPERT SYSTEM

Authors: K B Langton, MSC, A Mathieu, M.D., R B Haynes, M.D., PhD, A M Holbrook, M.D., S Cohen, B.S.
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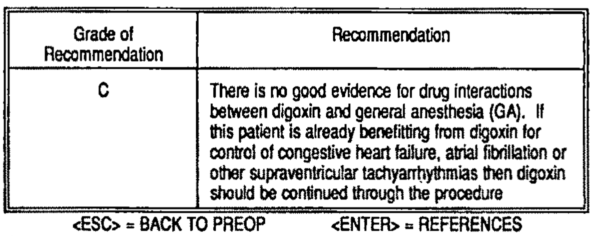
Introduction: Supply of medical information is currently deficient with respect to efficiency, effectiveness and economy. The use of "expert systems" may remedy this situation. Criteria for predicting the probability of postoperative cardiac complications of non-cardiac surgery, using cardiac risk factors[1] have been incorporated into a knowledge-based computer program, PREOP.[2] PREOP can assess cardiac risk factors, determine the probability of postoperative cardiac complications and recommend how to manage medications in the perioperative period. Additionally, if there are any potential interactions between preoperative medications and anesthetics, recommendations as to the prevention can be included.

Methods: PREOP was created using a computer program to facilitate its development (Nexpert Object). The program makes use of both rules and object-oriented programming techniques. PREOP works as follows: patient data such as age, specific medical history, physical exam, diagnostic tests, medication profile, and the type and urgency of the surgical procedure are entered; alternatively, this information could be extracted from the hospital's patient database. Thereafter, PREOP calculates the risk of drug interaction(s) and the probability that the patient will develop an adverse cardiac event during or after surgery and makes appropriate recommendations based on the level of evidence[3], in a report form that can be added to the patient's chart. All currently used cardiovascular drugs with potential interactions with anesthetics were investigated using a thorough literaterature search with Medline.

Results: This figure represents an example of a PREOP frame for one potential drug interaction.

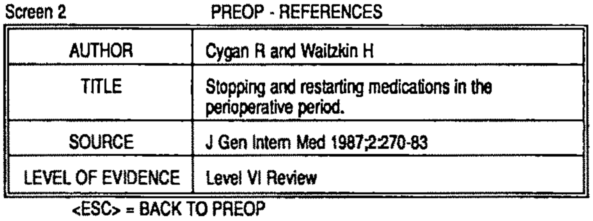
Boolean condition: if medications = digoxin & anesthesia = general (GA) then



Screen 1 PREOP - ONELINE RECOMMENDATION

Grade of Recommendation	Recommendation
C	There is no good evidence for drug interactions between digoxin and general anesthesia (GA). If this patient is already benefitting from digoxin for control of congestive heart failure, atrial fibrillation or other supraventricular tachyarrhythmias then digoxin should be continued through the procedure

<ESC> = BACK TO PREOP <ENTER> = REFERENCES



Screen 2 PREOP - REFERENCES

AUTHOR	Cygan R and Waitzkin H
TITLE	Stopping and restarting medications in the perioperative period.
SOURCE	J Gen Intern Med 1987;2:270-83
LEVEL OF EVIDENCE	Level VI Review

<ESC> = BACK TO PREOP

Discussion: We have described a practical approach to present and grade recommendations according to the quality of the supporting evidence. Such representation facilitates the user's critical appraisal and allows updating of the knowledge.

References: 1. J Gen Intern Med, 1:211-219, 1986.
2. Proc Second IASTED, ACTA Press pp. 167-170, 1990.
3. SCAMC Proc, 1991 in press.

S173

Title: PUPILLARY AND HEMODYNAMIC RESPONSES TO PAINFUL STIMULATION DURING ISOFLURANE ANESTHESIA

Authors: M Larson, M.D., DI Sessler, M.D., D Washington, M.D., Marie Prager, M.D., B Merrifield, B.A., J McGuire, B.S.

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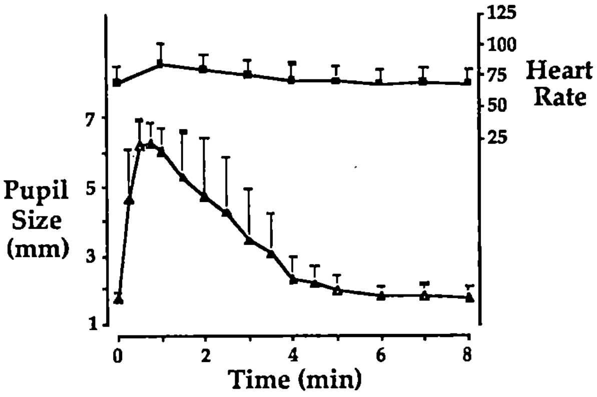
Pupil size correlates with end-tidal isoflurane concentration and plasma propofol concentration,[1] and thus may be useful during general anesthesia as an indicator of "anesthetic depth." We therefore examined the effect of a noxious stimulus on pupil size in eight volunteers anesthetized with isoflurane, but not undergoing surgery. Anesthesia was induced with isoflurane and N_2O, and maintained with 1.2% end-tidal isoflurane. A supra-maximal noxious stimuli was provided by needle electrodes placed in the skin of the abdomen and a 60 mA, 100 Hz current of 5 sec duration. Pupil size was measured using a portable infrared pupillometer (Fairville Medical Optics, Inc). Arterial blood pressure and heart rate were determined oscillometrically. Maximal dilation occurred 1-3 min following each stimulus. In marked contrast to the 3-4-fold increase in pupil size following stimulation, heart rate remained within 15% of control values (Fig.). Blood pressure increased even less than heart rate. Pupil size was far more sensitive to noxious stimuli than blood pressure and heart rate, suggesting that pupil size may better indicate anesthetic level than hemodynamic responses during isoflurane anesthesia.



Legend: Pupil size and heart rate in volunteers given supra-maximal stimulation during 1.2% isoflurane.

Reference: 1) Anesthesiology 75:62-67, 1991 and unpublished data.

Supported by NIH grant #R29 GM39723.

S174

TITLE: AUTONOMIC REFLEX DYSFUNCTION IN CARDIAC SURGERY PATIENTS MAY PREDICT HYPOTENSION AT INDUCTION

AUTHORS: T Latson MD, T Sakai MD, C Whitten MD
AFFILIATION: Department of Anesthesiology, UT Southwestern Medical Center, Dallas, TX 75235

INTRODUCTION: Autonomic reflex dysfunction in diabetics is associated with an increased incidence of hypotension at induction.[1] We investigated whether autonomic dysfunction in patients with cardiovascular disease similarly influences the response to induction. Preoperative autonomic function was assessed by spectral analysis of small oscillations in heart rate ("heart rate variability" or HRV) associated with autonomic reflex activity.[2]

METHODS: After institutional approval and informed consent, we studied 18 patients undergoing coronary bypass surgery; patients receiving insulin were excluded. Following lorazepam premedication (2-4mg IM) and insertion of radial and pulmonary artery catheters, EKG recordings for HRV analysis were obtained with patients in both supine and 45° head-up tilt positions. Anesthesia was then induced with sufentanil 1.5μg/kg and midazolam 0.1 mg/kg administered IV over 30 seconds. After loss of consciousness, patients were given vecuronium 0.1-0.15 mg/kg IV and ventilated by mask with 100% O_2 until intubated. Systolic blood pressure less than 90 mmHg was treated with phenylephrine(PHE).

A heart rate signal was derived from the digitally-recorded EKG.[3] Power spectral analysis of this signal was used to determine HRV spectral power in defined frequency ranges[4] (similar to analysis of the EEG).

RESULTS: Patients were divided into 2 groups based on the use of PHE prior to intubation: group P (PHE required, n=10) and group N (No PHE required, n=8). Whereas 7 of 8 patients in group N exhibited a normal increase in total low frequency HRV (HRVLO: 0-0.15Hz) with tilt, 8 of 10 patients in group P had no change or a decrease in HRVLO with tilt ($p<.02$, Fisher exact probability test). Mid-frequency HRV (HRVMID:0.07-0.15Hz) was also significantly less in group P patients when both supine ($p<.02$, Wilcoxon signed-ranks test) and tilted ($p<.002$). Groups P and N did not differ with respect to preinduction hemodynamics or frequency of: beta-blocker therapy, history of hypertension, depressed ventricular function, adult-onset diabetes.

DISCUSSION: These results document that differences in autonomic reflex function among patients presenting for elective cardiac surgery significantly influence the hemodynamic response to induction with a potent narcotic technique. Retrospective analysis suggests that absence of the normal increase in HRVLO (an index of sympathetic activity) with head-up tilt would have predicted hypotension at induction with a sensitivity of 80% and specificity of 88%. Additional prospective studies are warranted to further assess the value of HRV measurements for predicting perioperative cardiovascular instability.

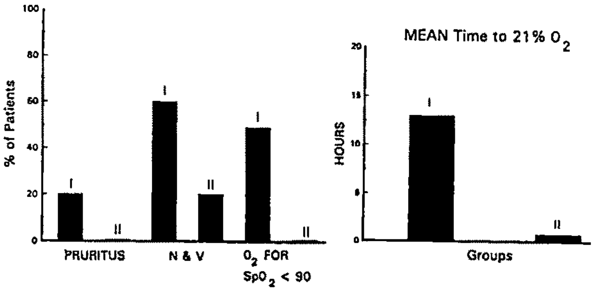
REFERENCES: 1)Anesthesiology 70:591, 1989; 2) Circ Res 59:178,1986; 3)IEEE Trans Biomed Eng 33:900, 1986; 4)Am J Cardiol 61:1292, 1988.

S175

Title: POSTOPERATIVE ANALGESIA IN PEDIATRIC PATIENTS UNDERGOING DORSAL RHIZOTOMY USING EPIDURAL MORPHINE WITH BUTORPHANOL

Authors: C.D. LAWHORN, M.D., F. BOOP, M.D., R.E. BROWN, MD., P. ANDELMAN, R.N.P.
Affiliation: DIVISION OF ANESTHESIOLOGY AND NEUROSURGERY, ARKANSAS CHILDREN'S HOSPITAL, LITTLE ROCK, AR

Dorsal rhizotomies for the unrelenting limb pain associated with spasticity are being performed with an increased frequency to improve posture, gait, and ambulation.[1,2] To aid in postoperative pain relief and to facilitate early physical therapy, epidural morphine and a morphine/butorphanol combination were evaluated in pediatric patients. In an ongoing study following IRB approval and informed parental consent, 9 patients were randomly assigned to 2 groups; Group 1 (80 mcg/kg epidural morphine), or Group 2 (80 mcg/kg epidural morphine with 40 mcg/kg epidural butorphanol). During surgical closure, a 20 gauge epidural catheter was placed by the operating surgeon. The study medication was administered in a randomized double-blinded fashion. Patients were evaluated every half hour for 4 hours and then every 4 hours for the next 72 hours recording respiratory rate, pulse rate, blood pressure, pulse oximetry and end tidal CO_2 ($ETCO_2$). Side effects and treatment were recorded. The patient was re-injected via the epidural catheter every 18 - 24 hours. Analysis of variance for repeated measure and the Newman Keuls test were performed for comparison between groups. Our results indicate that epidural narcotics provide excellent analgesia for postoperative pain following dorsal rhizotomy. The addition of butorphanol to morphine significantly decreases the incidence of side effects, minimizes changes in the CO_2 response curve and the decreases in oxygen saturation that occur with epidural morphine. Epidural morphine with butorphanol is an effective adjunct to the treatment of postoperative pain in the pediatric population.



References
1. J of Pediatrics 113:3,421-429, 1988
2. Child's Nerve Syst 5:337-346, 1989
3. Anesth Analg 72:53-57, 1991

S176

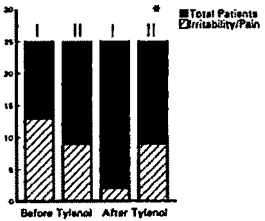
Title: TOPICAL LIDOCAINE FOR POSTOPERATIVE ANALGESIA FOLLOWING MYRINGOTOMY TUBE PLACEMENT

Authors: C.D. LAWHORN, M.D., C. BOWER, M.D., R.E. BROWN, JR., M.D., P. ANDELMAN, R.N.P.
Affiliation: DIVISION OF PEDIATRIC ANESTHESIOLOGY, DIVISION OF PEDIATRIC OTOLARYNGOLOGY, ARKANSAS CHILDREN'S HOSPITAL, LITTLE ROCK, AR

Myringotomy tube placement in infants and children is one of the most common procedures performed. Considerable irritability and pain have been associated with this surgery manifesting in the first hour of the recovery period. Opiates and analgesics have been used in the treatment of this pain, however they carry the possibility of sedation and increase recovery room stays. Therefore, lidocaine applied topically to the tympanic membrane prior to myringotomy was evaluated for efficacy in postoperative analgesia in this patient population.

Following IRB approval and informed parental consent, 50 ASA category 1 or 2 patients, between the ages of 6 months and 10 years, were randomly assigned to Group 1 (normal saline) or Group 2 (4% lidocaine). Following induction of general anesthesia, 0.5 cc of study solution was placed in the external auditory canal in direct contact with the tympanic membrane for 1 minute, aspirated from the canal, and the surgical procedure performed. Patients were evaluated using vital signs, pulse rate, blood pressure, crying, restlessness, agitation, irritability, using a scaled scoring system and VAPS when appropriate. Patients complaining of pain or a point score of 2 or more, were treated with rectal tylenol.

Results showed 13/25 patients in Group 1 (saline) exhibited subjective scoring indicative of irritability/pain or directly complained of pain. They were treated with rectal analgesics. Eleven of 13 patients had stable vital signs and decreased irritability pain scores following tylenol administration. In Group 2 (lidocaine), 0/25 patients complained of pain. Subjective irritability/ pain scoring was seen in 9/25 patients and received rectal tylenol. Of the 9 patients in Group 2 which received rectal analgesics, 0/9 had changes in irritability/pain score or vital signs ($p < 0.01$) compared to Group 1. We conclude that there is difficulty in differentiating irritability and pain during immediate postoperative period in this pediatric population and that 4% lidocaine applied topically appears to decrease the incidence of postoperative pain.



* $p < 0.01$

References
1. Drugs 18:185-205, 1979

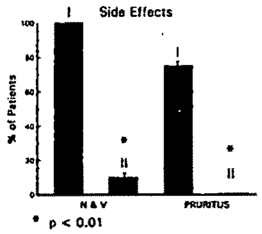
S177

Title: EPIDURAL MORPHINE WITH BUTORPHANOL FOR POSTOPERATIVE ANALGESIA IN PEDIATRIC PATIENTS UNDERGOING THORACIC PROCEDURES

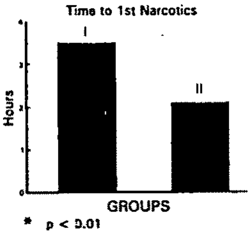
Authors: C.D. LAWHORN, M.D., S. GOLLADAY, M.D., R.E. BROWN, M.D., P. ANDELMAN, R.N.P.
Affiliation: DIVISION OF PEDIATRIC ANESTHESIOLOGY AND SURGERY, UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES, ARKANSAS CHILDREN'S HOSPITAL, LITTLE ROCK, AR

Epidural morphine has been used to provide a long duration of postoperative analgesia following upper abdominal, thoracic, and obstetrical procedures. The occurrence of side effects including pruritus, nausea, vomiting, respiratory depression and urinary retention have been a deterrent to the use of epidural morphine, especially in the pediatric population. Recently several studies have shown the efficacy of epidural butorphanol in decreasing the incidence of these side effects. Therefore, we evaluated the addition of butorphanol to epidural morphine in patients undergoing pectus excavatum repairs.

Following IRB approval and informed parental consent, 9 patients were randomly assigned to receive either morphine or morphine/butorphanol. Following induction of anesthesia, an epidural catheter was placed and study medications were administered in a randomized double-blinded fashion. Group 1 received preservative free epidural morphine 80 mcg/kg and Group 2 received preservative free epidural morphine 80 mcg/kg plus 40 mcg/kg of butorphanol. Patients were evaluated for the next 24 hours using respiratory rate, pulse rate and blood pressure. Pulse oximetry and end tidal CO_2 ($ETCO_2$) were similarly recorded, but continuously monitored. Patients completed a visual analog pain scale at intervals during the 24 hour observation period. Analysis of variance for repeated measures and Newman Keuls test were used for statistical analysis. No significant differences were noted in $ETCO_2$, SpO_2, or incidence of urinary retention. Our results indicate that epidural morphine with butorphanol increases the time to first narcotic use ($p < 0.02$), and decreases pruritus ($p < 0.01$), and nausea & vomiting ($p < 0.01$), associated with the use of epidural morphine in patients undergoing pectus repair.



* p < 0.01



* p < 0.01

References
1. Anesth Analg 72:53-57,1991
2. J of Pediatrics 113:3:421-429,1988

S178

Title: CELLULAR AND NONSPECIFIC IMMUNE FUNCTION AND OUTCOME AFTER ANESTHESIA WITH ISOFLURANE IN MICE

Authors: A.J. Layon, MD; L.F. Aleixo, MD; A.B. Peck, PhD; R.J. Howard, MD
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Decades of work suggest that in-vitro immune defects occur perioperatively (1). The most recent work (2) points to calcium mobilization abnormalities in neutrophils after exposure to isoflurane. No data, however, indicate whether these defects alter outcome. We hypothesized that, in a healthy model, if the immune system, like other organs, has functional reserve, a measurable, in-vitro immune defect induced by certain anesthetic agents would not affect outcome.

With institutional approval, we studied BALB/c male and nonpregnant female mice. All mice were handled in the same way regardless of experimental grouping, and light and dark cycles were kept constant. Mice were or were not (control) exposed to 1.8% isoflurane (130% MAC) for 1.5 hr and killed immediately or 1, 12, or 24 hr afterwards (n = 40/group). Antigen paradigms (3) were polyclonal T- and B-cell activators (PCAs)—lypopolysaccharide (LPS), concanavalin A (con A), phytohemaglutinin, and poke-weed mitogen (PWM). In a second set of mice that were or were not (control) exposed to isoflurane (n = 32/group) according to the same regimen as above, 4.5 x 10^7 E. coli were injected intraperitoneally, as a paradigm of sepsis and to test nonspecific immune function. Concentration of the organism came from previous survival experiments. Activity stimulated by PCAs was measured by counts/min ^{3}H-thymidine uptake (4-hr pulse) after culture for 68 hr (mean ± 1 SD). E. coli-exposed animals were followed for 7 days, and the number dead were compared. Univariate procedure for normality, Wilcoxon, and Fisher's exact analyses were used; $p < 0.05$ was considered significant.

Exposure to isoflurane resulted in no measurable in-vitro T- or B-cell immune defect. Nonspecific immune function, measured by outcome after a sublethal E. coli challenge was not adversely affected ($p = 0.29$).

Our data suggest that, in spite of previous findings (4), no measurable defect in immune function exists after exposure to isoflurane alone. Whether this is so in immune compromised animals is yet to be seen.

References
1. Trauma, Stress and Immunity in Anaesthesia and Surgery. London: Butterworths, 1982:211-3.
2. Anesthesiology 1986; 64:4-12.
3. Eur J Immunol 1977; 7:451-7.
4. Cell Immunol 1972; 4:381-93.

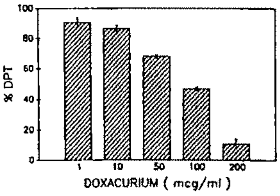
S179

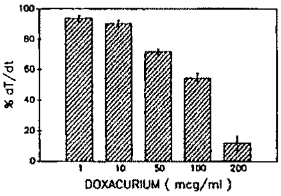
Title: NEGATIVE INOTROPISM OF DOXACURIUM IN RABBITS

Authors: TS Lee, M.D., XH Hou, M.D., Y Lin, M.D., M Lippmann, M.D.
Affiliation: Harbor-UCLA Med. Center, 1000 W. Carson St, Torrance, CA, 90509

Doxacurium is one of the newly available long acting nondepolarizing muscle relaxants. The cardiovascular stability with its administration has been demonstrated in several studies and is considered an advantage over pancuronium[1-3]. It also does not release histamine. In this study, we investigate the direct effect of doxacurium on myocardial contractility in isolated rabbit myocardium.

Seven New Zealand white rabbits, weighing 2-3 kg were anesthetized with 45 mg/kg intravenous pentobarbital. The heart was immediately removed. The first septal perforator of the left coronary artery was cannulated and perfused with warmed (37°C) oxygenated modified Kreb Ringer bicarbonate buffer (KRB) solution at 1 mg/gm/min. The septum was then dissected out and suspended from a Grass FT03 tension transducer. A 5-volt/5 msec electrical stimulation was given from a Grass stimulator at 1.6 Hz. After reaching fully stabilized contractions for at least 30 min, perfusion of doxacurium diluted in KRB solution was started with concentrations of 1, 10, 50, 100 and 200 mcg/ml, respectively. Each dosage was given for 5 min, and the plain oxygenated KRB solution was perfused in between as the control. The peak developed tension (PDT), the maximal acceleration (±dT/dt), time to peak tension (TPT), and time to ½ tension relaxation (RT½) were recorded and calculated as % of control values. The results were analyzed with paired t-test and summarized in Table I.





Clinically, doxacurium has been shown to have no significant side effect on hemodynamic variables at doses up to 3 times its ED95[1], and appears to be a safe drug for use in patients with cardiac disease[2]. However, our study demonstrated that doxacurium had a significant dose-related myocardial depressant effect in isolated rabbit myocardium. We suggest that some precautions should be exercised to avoid overdose in patients with significant myocardial insufficiency.

References:
1. Anesthesiology 69:365-370, 1988
2. Br J Anaesth 63:675-681, 1989
3. Br J Anaesth 65:480-486, 1990

S180

TITLE: THE DIRECT EFFECTS OF MIDAZOLAM ON MYOCARDIAL CONTRACTILITY IN RABBITS

AUTHORS: TS Lee, M.D., Y Lin, M.D., B Chen, M.D., D Hsu, M.D.
AFFILIATION: Anes. Dept., Harbor-UCLA Med. Center, Torrance, CA 90509

Serious cardiorespiratory adverse events have been reported following midazolam's administration, particularly in elderly, debilitated patients. These have included circulatory collapse and/or cardiac arrest, sometimes resulting in death. In this study, we investigated the direct effects of midazolam on myocardial contractility in an isolated rabbit myocardial septum preparation.

Nine New Zealand white rabbits, weighing 2-3 kg were anesthetized with 45 mg/kg intravenous pentobarbital. The heart was immediately removed. The first septal perforator of the left coronary artery was cannulated and perfused with warmed (37°C) oxygenated modified Kreb Ringer bicarbonate buffer (KRB) solution at 1 mg/gm/min. The septum was then dissected out and suspended from a Grass FT03 tension transducer. A 5-volt/5 msec electrical stimulation was given from a Grass stimulator at 1.6 Hz. After reaching fully stabilized contractions for at least 30 min, perfusion of midazolam diluted in KRB solution was started with concentrations of 0.1, 1, 10 and 100 mcg/ml, respectively. Each dosage was given for 5 min, and the plain oxygenated KRB solution was perfused in between as the control. The peak developed tension (PDT), the maximal acceleration (±dT/dt), time to peak tension (TPT), and time to ½ tension relaxation (RT½) were recorded and calculated as percent of control values. The results were analyzed with paired t-test and summarized in Table I.

MIDAZOLAM (mcg/ml)	0.1	1	10	100
PDT%	96.9±1.9	95.1±2.1	79±1.3*	10.1±1.2*
+dT/dt%	96.5±2.6	94.2±1.7	77±1.6*	9.8±1.7*
-dT/dt%	93.4±2.5	93.4±1.9	79±2.4*	7.8±0.9*
TPT%	97.8±1.6	96±1.3	90.8±1.6*	76.5±2.1*
RT½%	96±2.0	91±1.7	88.5±2.9*	71.5±3.0*

TABLE I: Mean ± SE, $*P < 0.05$

Our study showed midazolam had a significant dose-related myocardial depressant effect. The decrease of PDT accompanied by reduction in dT/dt, TPT and RT½ may be related to the rate of Ca++ availability to troponin, the quantity of Ca++ delivered to the myofilaments and the rate of Ca++ removal from the contractile sites. Central line bolus administration of midazolam should be avoided.

References:
1. Anesth. Analg., 1987, 66:711-8
2. Anesthesiology 1984, 60:717-8

S181

Title: KETOROLAC GIVEN PRIOR TO ARTHROSCOPIC KNEE SURGERY DECREASES POSTOP PAIN SCORES AND NARCOTIC DOSES

Authors: Lee VC, M.D., Kendrick WD, M.D., Brown NW, M.D., Harman AM, M.D., Grove GW, M.D.
Institution: Department of Anesthesiology, University of Virginia Health Sciences Center, Charlottesville, VA 22908

Introduction: Administration of a nonsteroidal anti-inflammatory drug (NSAID) prior to surgery offers the possible advantage of prostaglandin inhibition prior to the onset of tissue trauma; this may reduce postoperative pain by preventing hyperalgesia induced by inflammatory mediators released from the traumatized tissue.[1] The following study examines the effect of the injectable NSAID ketorolac tromethamine upon postop pain scores in ambulatory surgical patients undergoing arthroscopic knee surgery.

Methods: With the approval of our Human Investigation Committee, twenty-one consenting patients undergoing arthroscopic knee surgery were randomized to receive 30 mg of ketorolac IV or saline placebo preop. A standardized general anesthetic was administered for surgery and local anesthetics were not used. Following emergence from anesthesia, patients were recovered and periodic assessments made of subjective pain (10 cm visual analog scale, or VAS) as well as observer ratings of pain, nausea, and sedation, each of which was given a 0-4 ordinal score (rank). The observer was blinded to the experimental condition. Postop narcotic (fentanyl in 25-50 mcg increments) was given as needed to control pain.

Results: The VAS's were compared for drug and placebo groups. The mean initial VAS was more than doubled in the placebo group (Table 1), significant at the p=.02 for the independent sample 2-tailed t-test; the other VAS's demonstrated a nonsignificant trend towards being likewise increased in the placebo group. Observer rated pain scores (pain ranks) were all significantly higher in the placebo group by Mann-Whitney U-test. Postop fentanyl requirement was nearly tripled in the placebo group (156 mcg) compared with the drug group (42.3 mcg), significant at p=.04 by Mann-Whitney U-test. On the other hand, recovery time and postop sedation scores were not different between groups. Incidence of nausea and vomiting were not significantly different by Fisher's exact test.

Conclusions: Ketorolac, 30 mg IV, given prior to arthroscopic knee surgery decreases postop pain scores as well as requirement for postop narcotics as demonstrated here. Sedation, incidence of nausea and vomiting, and recovery times were not significantly different between groups.

Table 1. Postop measurements which differ significantly between ketorolac and placebo pretreated patients

	Drug Group	Placebo Group	P value*
n	13	8	
VAS (0 min)	2.3 ± .6 SE	5.1 ± 1.0	.02
Pain Rank (0 min)	.5 ± .2	1.6 ± 1.2	.02
Pain Rank (40 min)	.9 ± .3	2.1 ± .5	.04
Pain Rank (max)	1.2 ± .2	2.5 ± .3	.01
Pain Rank (final)	.5 ± .1	1.1 ± .3	.03
Fentanyl Dose (mcg)	42.3 ± 15.6	156 ± 50	.04

*see text for statistical methods

Reference:

1. Huang KC, Wolfe WM, Tsueda K, et al: Effects of meclofenamate and acetaminophen on abdominal pain following tubal occlusion. Am J Obstet Gynecol 1986;155:624-629.

S182

Title: WHOLE-BODY OXYGEN DELIVERY IN DOG DURING HEMODILUTION AND DELIBERATE HYPOTENSION

Authors: C. LEJUS, M.D., JM. BERNARD, M.D., Y. BLANLOEIL, M. D., P. BIZOUARN, M.D., M. PINAUD M.D.
Affiliation: Lab. Anesth. Faculté de Médecine.44035 Nantes France.

Introduction: This study examined the effects of combination of 2 methods of sparing transfusion, hemodilution and deliberate hypotension in dog.

Methods: 7 dogs were anesthetized by 0.5 MAC of isoflurane in air and mechanically ventilated in order to maintain normocapnia. After insertion of aortic and fiberoptic pulmonary artery catheters, 500 (H1) and 1000 (H2) ml of blood was replaced by equal volume of 6% dextran 60 solution. At each diluted state, a 50 % decrease in MAoP was induced, successively in randomized order, by nitroprusside (NPS) and by increasing isoflurane (ISO). Hemodynamics, blood gases and plasma lactate concentrations (Lac) were measured, before and after 20 min. stable hypotension, at each level of dilution, i. e. non hemodiluted state (N), H1 and H2. Statistics were ANOVA, followed by T-tests. $p<0.05$ was considered as significant.

Results: There were no interactions between hemodilution and treatments (NPS, ISO and no hypotension), allowing us to appreciate the mean effects of hemodilution: H1 did not change oxygen extraction (OER). Despite further increase in cardiac output (CO), H2 led to increase in OER and Lac (Table). Although at each diluted state, CO was lower during ISO than during NPS, no difference in OER and Lac were found between treatments (Figure).

Discussion: Our results suggest that 1) whole-body oxygen delivery becomes inadequate below a wide range of hemoglobin levels, but 2) in such a situation, delivery is not influenced by changes of CO due to the type of hypotension.

Table

	N	H1	H2
Hb (g/dl)	10.2 ± 0.4	6.3 ± 0.3*	3.2 ± 0.2*°
CO (l/min)	3.6 ± 0.3	5.1 ± 0.4*	7 ± 0.5*°
SvO2 (%)	77 ± 1	73 ± 2	61 ± 2*°
OER (%)	22 ± 2	26 ± 2	32 ± 2*°
Lac (mml/l)	1.7 ± 0.2	2.1 ± 0.2	2.9 ± 0.2*°

mean ± SD. * vs N. ° vs H1

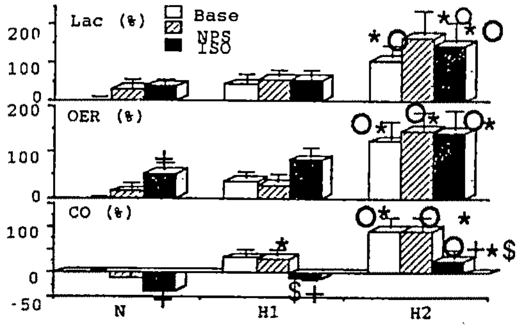


Figure: * vs N, ° vs H1 with equivallent treatment (Base, ISO or NPS); + vs Base, $ vs NPS with equivallent dilution (N, H1 or H2).

S183

Title: POSTOPERATIVE INTRAVENOUS CONTINUOUS ANALGESIA : BUPRENORPHINE (B) VS FENTANYL (F) VS NALBUPHINE (N).

Authors: C. LEJUS M.D., Y. BLANLOEIL M.D., T. FRANÇOIS M.D., P. REVERDY M.D., S. TESTA M.D., P. MICHEL M.D..

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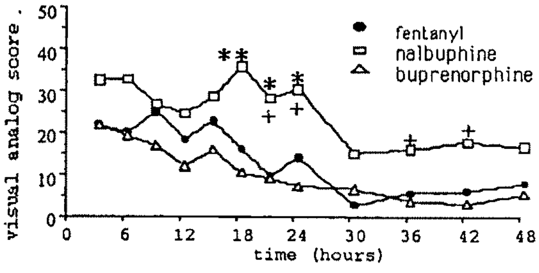
Introduction: The aim of this study was to compare N, F and B, given by continuous I.V. infusion (CIV) for postoperative analgesia after major abdominal surgery.

Methods: Under the approval of our Human Investigation Committee, 61 Intensive Care Unit patients aged 58 ± 14 yrs who had undergone abdominal or thoraco-abdominal surgery were randomized in three groups. In group 1 (n=23), B was given as a loading dose of 5 $\mu g.kg^{-1}$ and infused at 0.8 $\mu g.kg^{-1}.h^{-1}$. In group 2 (n=19), F was given as a loading dose of 2 $\mu g.kg^{-1}$ and infused at 0.7 $\mu g.kg^{-1}.h^{-1}$. In group 3 (n=19), N was given as a loading dose of 200 $\mu g.kg^{-1}$ and infused at 80 $\mu g.kg^{-1}.h^{-1}$. Postoperative pain assessment was performed at 3 h (during the first 24 h) and 6h intervals (during the following 24h) with visual analog pain scale (VAS) graded from 0 to 100. Overall sedation was assessed after 48h, with a 4 point scale. When analgesia was inadequate (VAS score >50) opiate infusion rate was increased by increments of 0.2 $\mu g.kg^{-1}.h^{-1}$(B), 0.3 $\mu g.kg^{-1}.h^{-1}$(F), 10 $\mu g.kg^{-1}.h^{-1}$(N). When weaning from the ventilator was rendered difficult by respiratory depression, the rate of opiate infusion was decreased to resume patient's spontaneous breathing. During this period in case of inadequate analgesia, propacetamol I.V. bolus was added. Data were analysed using Kruskal-Wallis analysis, Mann and Whitney U tests. All values are mean ± SD.

Results: There was no difference between groups in demographics and sedation. The 48h mean doses were respectively 0.74 ± 15 $\mu g.kg^{-1}.h^{-1}$.(B), 0.68 ± 0.18 $\mu g.kg^{-1}.h^{-1}$(F), 83 ± 21 $\mu g.kg^{-1}.h^{-1}$.(N). VAS scores are summarized in the figure. Only 8 patients in group 3 received propacetamol (4g/24h). Respiratory depression occured for 6 patients in group 2 and 8 patients in group 1. No respiratory depression occured after extubation.

Discussion: CIV F and B provided better postoperative analgesia than N allowing spontaneous breathing with smaller doses than those reported in similar studies (1,2).

References: 1 Br. J. Anaesth., 59:1364-1374, 1987.
2 Br. J. Anaesth., 60:608-613, 1988.



* p< 0.05 F vs N, **p<0.01 F vs N, +p<0.05 B vs N

S184

Title: NEURAL-NETWORK BASED CALCULATION OF WORK OF BREATHING DURING PRESSURE SUPPORT VENTILATION

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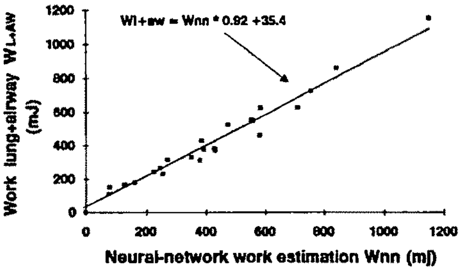
Introduction: This experiment investigated the accuracy of a neural-network based method for estimation of spontaneous inspiratory lung and airway work of breathing (W_{L+AW}) during pressure support (PS) ventilation (PSV).

Methods: A two-bellows mechanical lung analog was modified for simulation of spontaneous breathing. Simulating the inspiratory muscles, a volume-controlled Servo 900C ventilator (Siemens-Elema, Sweden) inflated one bellows, which represented the chest wall. This bellows was connected to the second bellows, the "lung" bellows, with a linking piece from which an analogous of the pleural was measured. The "lung" bellows inlet was connected to the circuit of a Bennet 7200ae ventilator (Puritan-Bennett, USA) set to deliver PSV. Experiments consisted of obtaining tidal volumes (300,400...800 ml) by applying graded levels of PS (0,2,...20 cm H_2O) and enough "muscular inspiratory effort" (minute volume) from the Servo 900C. When a target volume was achieved, mean inspiratory airway pressure (PAW_{mean}), peak and mean inspiratory flow ($\dot{V}_{peak}$, $\dot{V}_{mean}$), and a function of the pleural pressure, $W_{EST}= SUM[(P_{PLmax} - P_{PL})* \dot{V}dt]$, were calculated and recorded. Then, all pressure support was discontinued, and the "spontaneous" work W_{L+AW} was calculated and recorded. Fifty determinations were recorded. A neural-network was defined to estimate inspiratory lung and airway work (W_{NN}) from PAW_{mean}, $\dot{V}_{peak}$, $\dot{V}_{mean}$, W_{EST}, and P_{PS}. Data from 25 trials were used for training the network. Once trained, the neural-network estimated W_{NN} for the remaining, "unseen", 25 trials. The results were compared to the real values of W_{L+AW}.

Results: A linear regression and correlation analysis between W_{L+AW} and W_{NN} resulted in a slope of 0.92 (S.E.=0.03), a Y-intercept of 34.5 (S.E.=16.7), and an R squared of 0.968. Data points and the best fitting straight line are shown in the Figure.



Discussion: During PSV, patient's work of breathing cannot be assessed directly, since inspiratory muscular pressure is usually unknown[1]. By using variables that are clinically available, the method described here accurately estimated W_{L+AW} in a PSV-spontaneous breathing model. Additional research is required to assess the validity of the method in living subjects. If applicable, neural-network technology may be used for monitoring work of breathing in patients receiving assisted modes of ventilation.

References:
1. CHEST 1985;87:612-618.

S185

Title: Plasma inorganic fluoride concentration in children anesthetized with Sevoflurane

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Affiliation: Dept of Anaesthesia and Research Institute, HSC, U of T, Toronto and Dept of Anesthesiology, U of A, Tucson*.

Introduction: Sevoflurane is a new potent inhalational ether anesthetic that is currently under investigation in children. It is defluorinated in vivo to a small extent, with the release of inorganic fluoride (F). Therefore, we investigated the concentration profile of inorganic F ([F]) in children anesthetized with sevoflurane.

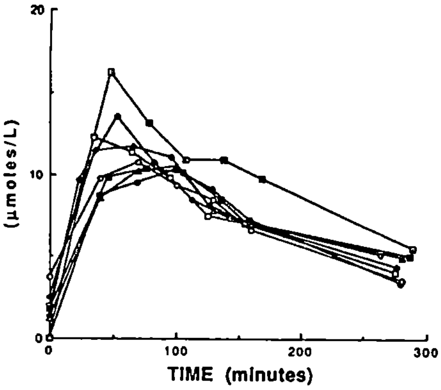
Methods: With institutional approval and consent, 8 healthy children 5-12 years of age were anesthetized with sevoflurane in oxygen and maintained with sevoflurane and 70% nitrous oxide in oxygen throughout surgery. Plasma was obtained at induction and discontinuation of anesthesia, and every 30 minutes after surgery for 2 hours and then at 4 hours for determination of inorganic [F]. Plasma [F] was determined by an Orion Ionanalyzer fitted with a fluoride-specific electrode.

Results: After 38 min of anesthesia, the maximum plasma inorganic [F] (mean ± sd) was 12.0 ± 2.1 µM. Peak plasma [F] occurred about one hour after surgery and decreased thereafter (figure). The area under the [F]-time profile (mean ± sd) was 33.3 ± 4.0 µM•h.

Discussion: In vivo metabolism of sevoflurane yields peak plasma [F] similar to enflurane[1] in children and well below accepted thresholds for nephrotoxicity. Areas under the [F]-time profile are well below those reported for methoxyflurane in children.[2] We conclude that the plasma [F] in children exposed to 0.6 MAC•h sevoflurane does not appear to pose a significant threat to renal function.

References:
1. Oikkonen M, Meretoja O. Eur J Anesth 6:401-7, 1989
2. Stoelting RK, Peterson C. Anesthesiology 42:26-29,1975

Acknowledgement: Supported in part, with a grant from Maruishi Pharmaceutical Inc, Japan



Plasma Fluoride Concentration

S186

Title: RECOVERY FROM ANESTHESIA AND CEREBRAL BLOOD FLOW VELOCITY

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Introduction: Arterial hypertension and hypercapnia occur frequently at the end of general anesthesia and can be critical to cerebral circulation. The purpose of this project was to evaluate cerebral blood flow changes during emergence with extubation and during recovery from anesthesia.

Methods: Following institutional approval ten patients (age 40.6 ± 14.4) were included in the study. Anesthesia was conducted with 50% N2O/O2, isoflurane, vecuronium and fentanyl. At the end of surgery neuro-muscular blockade was reversed and extubation performed. The middle cerebral artery flow velocity (MCAFV) was measured at the temporal window (1) using a TCD 2-54B system and recorded via video graphic printer. Pulsatility index (PI) was calculated using the formula adopted from Pourcelot's index of resistance. The MCAFV, mean arterial blood pressure (MABP), and end-tidal CO2 (PETCO2) were recorded during anesthesia, during emergence with extubation, and one hour later. Oxygenation and temperature were controlled during the study.

Results: The vm in MCA and PI during anesthesia were 44.2 ± 11.8 cm/s and 0.81 ± 0.14 respectively. MABP was 78.9 ± 5.8 mmHg and PETCO2 29.5 ± 2.7 mmHg. At emergence and extubation vm increased to 113.0 ± 19.8 cm/s ($p<0.001$) and PI dropped to 0.51 ± 0.09 ($p<0.002$). At the same time MABP reached 107.2 ± 10.1 mmHg and PETCO2 41.0 ± 4.1 mmHg. One hour later vm and PI were 72.2 ± 16.9 cm/s and 0.79 ± 0.18 respectively with MABP and PETCO2 being 101.2 ± 6.2 mmHg and 40.3 ± 4.5 mmHg.

Discussion: The arterial hypertension and increase of PETCO2 during emergence from anesthesia were accompanied by decrease in cerebrovascular resistance (PI) and a dramatic increase in MCAFV (by 155%). The impairment of autoregulation (2) and enhancement of CO2 reactivity (3) by anesthetics could play a role in this response. During first hour of recovery cerebrovascular resistance increased and MCAFV returned to near-physiologic value.

References:
1. Aaslid R.: TCD, Springer-Verlag, New York, 1986.
2. Anesthesiology, 69, 3A, 533, 1988.
3. Anesthesiology, 71, 3A, 104, 1989.

S187

Title: THE ACCURACY OF THE EEG IN PREDICTING HEMODYNAMIC CHANGES WITH INCISION DURING ISOFLURANE ANESTHESIA

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INTRODUCTION: Electroencephalographic variables derived from power spectrum analysis (PSA) have been used to determine anesthetic depth. One such descriptor, the spectral edge frequency (SEF), has been found to correlate with hemodynamic changes during surgery (1). Bispectral analysis, which quantifies nonlinear interactions and phase coupling of different frequencies, may provide information that is not available with more conventional means of analysis. The purpose of this study was to determine whether or not hemodynamic and EEG changes with inicision could be correlated with level of isoflurane anesthesia (as defined by multiples of minimum alveolar concentration of volatile anesthetic (MAC).

METHODS: After obtaining approval from the Human Rights and Research Committee, consent was obtained from 14 patients, ASA I-II, ages 22-57, and undergoing elective surgical procedures. Upon arrival to the operating room, intravenous access was established and routine monitors applied. A continuous 4 channel EEG was recorded (CH1: Fp1-F3, CH2: Fp2-F4, CH3: P3-O1, CH4: P4-O2, Ref Fp). Patients underwent an inhalation induction with oxygen, nitrous oxide and isoflurane. Intubation was facilitated with vecuronium (0.1 mg/kg) and ventilation was controlled to maintain normocarbia. Patients were randomly assigned to receive maintenance anesthesia of 1.0, 1.5 or 2.0 MAC isoflurane in 100% oxygen. After a period of at least 15 minutes of stable anesthesia, as documented with an end-tidal agent monitor, surgery was begun. Blood pressure and pulse were recorded every 2 min from 5 min prior to incision. The EEG was recorded continuously using a microcomputer (Biometrak Corp.) and analyzed off line for 95% SEF, median frequency, delta, and a discriminate bispectral parameter. The three anesthetic dose groups were compared using ANOVA and the responders and non-responders (ΔBP < 20%) were compared using a group T test.

RESULTS: Anova showed no significant effect of anesthetic concentration on any of the EEG measures shown in the table. However, the value of the discriminate bispectral parameter was different for responders (ΔBP>20%) and non-responders (ΔBP<20).

EEG Descriptor	Responders (+/-SD)	Non Responders (+/-SD)	P
Delta Power	-3.65 (0.77)	-2.54 (1.12)	0.061
SEF (Hz)	15.5 (2.2)	14.9 (4.7)	0.052
Median Freq. (Hz)	5.17 (1.50)	3.62 (1.18)	0.792
Discriminate Bispec.	0.57 (0.91)	-1.34 (1.05)	0.005

There were no statistically significant differences in the degree of blood pressure change on incision at each level of anesthesia as shown below:

Anesthetic	ΔBP (+/-SD)
1 MAC	21.0 (4.2)
1.5 MAC	12.3 (17.2)
2 MAC	27.5 (30.5)

The sensitivity, specificity and overall predictive accuracy of EEG descriptors were as follows:

EEG Descriptor	Sens	Spec	Acc
Delta Power	67%	88%	79%
SEF	100%	50%	71%
Median Frequency	67%	88%	79%
Discriminate Bispec.	80%	88%	85%

CONCLUSIONS: In this study, the degree of blood pressure change with incision could not be predicted based on conventionally defined (MAC) levels of anesthesia. However, the value of the discriminate bispectral EEG parameter did correlate with the increases in blood pressure seen with incision. These findings correlate well with those previously reported where the bispectrum of the EEG predicted movement in response to incision (2). Bispectral analysis appears to improve the overall accuracy of the EEG and therefore may prove to be a useful tool in the assessment of the anesthetic depth.

REFERENCES:
(1) Anesthesiology 1987, 67:139-142.
(2) Anesthesiology 1991 (suppl.), in print.

S188

TITLE: PANCURONIUM PRETREATMENT PROLONGED RECOVERY INDEX OF VECURONIUM IN CHILDREN.

AUTHORS: M.L. Lin, M.D., S.K. Tsai, M.D., M.S. Mok, M.D.
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Vecuronium, a short acting non-depolarizing muscle relaxant, often is used interchangeable with pancuronium, the long acting depolarizer with a chemical structure closely related to vecuronium.

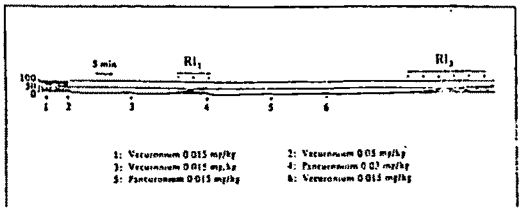
The present study was undertaken to evaluate the recovery index of vecuronium administered after a prior dose of pancuronium in pediatric patients.

After obtaining parental consents 15 children of ASA class I-II physical status with age ranging from 3-7 years who underwent dental procedures were enrolled into the study. All patients were premedicated with atropine 0.01 mg/kg I.V. and anesthetized with halothane-N_2O-O_2 by mask. Supramaximal train-of-four ulnar nerve stimulation was applied with Datex Relaxograph at every 20 seconds for electromyographic (EMG) response from the adductor pollicis muscle. Intubation was accomplished with the priming dose of vecuronium 15 mcg/kg I.V. followed by vecuronium 50 mcg/kg I.V. 6 minutes later. Recovery index (RI) defined as the time required for 25% to 75% spontaneous T_1 twitch recovery is measured after a maintenance dose of vecuronium 0.015 mg/kg was given. (Fig.1). Then pancuronium 0.03 mg/kg I.V. was given. When T_1 twitch showed 25% recovery as shown at point 6 of Figure 1, a single dose of vecuronium 0.05 mg/kg I.V. was given and the recovery index is once again measured. The recovery index of vecuronium when administered as the sole muscle relaxant was 11.5 ± 3.0 minutes, whereas the RI of identical dose of vecuronium after pretreatment of pancuronium was 24 ± 6.4 minutes.

Discussion:

In clinical practice the anesthetist often elects to use vecuronium near the end of surgery when the patients are partially recovering from pancuronium induced neuromuscular block in the hope that vecuronium will provide a muscle relaxation of brief duration which is often needed for surgical closure. Our study showed that recovery index of vecuronium was much prolonged after a preceding dose of pancuronium. This perhaps explains the "unexpected" and "unusual" long duration of action with such a dose of vecuronium frequently observed in the clinical setting. Hence a reduced dose of vecuronium is needed in order to avoid "inadvertent overdose" resulting in delay of recovery.

FIG.1 EMG TWITCH TRACING WITH DIFFERENT MEDICATIONS



S189

TITLE: HEMODYNAMIC EFFECTS OF WARM CARDIAC IRRIGATION

AUTHORS: N Lingaraju MD, P Colonna MD, JC Horrow MD, M Strong MD
AFFILIATION: Depts of Anesthesiology and Cardiothoracic Surgery, Hahnemann Univ., Philadelphia, PA 19102-1192

Following cardiopulmonary bypass (CPB) and prior to closing the chest, some surgeons irrigate the heart and pericardium with warm saline. Although this maneuver affects hemodynamics, we can find no studies describing those effects. This prospective study evaluates the hemodynamic effects of warm irrigation of the heart and pericardium following CPB, using each patient as his own control.

METHODS

With IRB approval, 11 patients undergoing CPB for cardiac surgery gave informed consent. Following CPB, Mon-a-therm model 6500 thermocouples measured the temperatures of the myocardial septum and of the warm saline for irrigation. Immediately prior to, during, and 2 min after immersion of the heart by pouring more than 1 liter of warm fluid into the pericardial cradle, we measured the patient's heart rate (HR), systemic blood pressure (BP), pulmonary artery pressure (PAP), central venous pressure (CVP), and thermodilution cardiac output (Marquette model 7000RA), Milwaukee, WI), with SVR calculated. Acceptable cardiac output (CO) measurements required at least one temperature *v.* time curve with stable baseline and appropriate shape. The temperature of the myocardium immediately following irrigation was also recorded. Statistical analysis employed repeated measures analysis of variance with Tukey's HSD test for pairwise comparisons. $P < 0.05$ determined significance.

RESULTS

The irrigation fluid was 44±5°C (SD), and ranged from 36.2°C to 48.9°C. Myocardial septum increased in temperature by 0.3± 0.2°C (range 0.0-0.7°C). The table displays the hemodynamic data. Analysis disclosed effects of measurement time on HR (P=.0005), systolic BP (P=.0147) and calculated SVR (P=.0076). During irrigation with warm saline, HR increased 9±8 (SD) bpm (P.0139) and systolic BP increased 20±22 mm Hg (P=.0359). SVR did not change significantly. After irrigation, HR decreased 5±6 bpm (P=.0124), returning to its pre-irrigation level. Although systolic BP did not change significantly between irrigation and post-irrigation measures (P=.191), the post-irrigation BP was within 13±24 mm Hg of the pre irrigation value. The SVR post-irrigation was 296±302 dynes·cm^{-5}·sec greater (P=.009) than its pre-irrigation value. CO after irrigation did not decrease significantly (P=.07).

Table. Hemodynamic changes upon warm cardiac irrigation. Entries are mean±SD

	Before	During	After
Heart rate	93 ± 15	101 ± 13**	96 ± 12*
Systolic BP	111 ± 17	131 ± 27**	124 ± 22
SVR	821 ± 243	956 ± 387	1117± 413**
C.O.	6.1 ± 1.7	6.4 ± 1.9	5.4 ± 1.6

**P*<.05 compared to "during"; ***P*<.05 compared to "before".

DISCUSSION

HR and BP rise during warm irrigation of the heart and pericardium, but return to their pre-irrigation values soon after the irrigation. SVR increases more slowly, reaching and maintaining a statistically significant level after the effects on HR and BP have dissipated. Post-operative myocardial ischemia occurs most frequently with 2 hrs of revascularization.[1] Increased myocardial oxygen demand from the tachycardia and elevated SVR arising from warm irrigation may exacerbate ischemic tendencies at this time. Future work might identify the source of this sympathetic response, whether from aortic, pericardial, myocardial, or other afferent receptors.

REFERENCES

1. Smith RC et al: Anesthesiology 74: 464,1991.

S190

TITLE: INTRAOPERATIVE VIGILANCE TOWARD A PHYSIOLOGIC MONITOR

AUTHOR: R.G. Loeb, M.D.
AFFILIATION: Dept. of Anesth., Univ. of California, Davis, Med. Ctr., Sacramento, CA 95817

Introduction. Electronic monitors display important intraoperative data. This study was performed to assess anesthetic vigilance to sudden and unexpected changes in physiologic parameters during actual anesthetic procedures.

Methods. After obtaining approval from our Human Subjects Review Committee, we studied the vigilance of 8 anesthesiology residents during 60 minor operative procedures. Each resident consented to participate and all knew that their vigilance was being assessed.

The resident was instructed to monitor a simulated display while conducting an anesthetic case. The display consisted of the word, "vig" above a numeric value on the screen of our standard physiologic monitor (Puritan Bennett model 240, Wilmington, MA). Two numeric values were displayed, one at a time, during each case. Normally, the lower value was displayed; but at random intervals the larger *abnormal* value was displayed. The experimental period began in the operating room when the EKG electrodes were attached and concluded at the end of the case when they were disconnected. When the resident observed an *abnormal* value, he pressed a button on the table of the anesthesia machine to redisplay the *normal* value. The number of seconds between the initiation of the abnormal display and the press of the button was recorded as a response time. If the button was not pressed after 5 minutes, the display reverted to the *normal* value, and the response was coded as "undetected".

Results. Responses to 439 abnormal values were analyzed. The average response time was 61 ± 61 seconds (mean ± SD) and 56% of the detections were made within 60 seconds. However, 16% of the abnormal values were undetected during the 5 minutes that they were displayed. Abnormal values were less frequently detected during induction than during the maintenance or emergence phases of anesthesia. The response time was also longer during induction (73 ± 68 seconds) than during maintenance (57 ± 60 seconds) ($P < 0.05$). Abnormal values were more frequently detected during procedures on healthier patients and the response times were shorter with ASA 1 patients (54 ± 54 seconds) than with ASA 3 patients (79 ± 72 seconds) ($P < 0.02$).

Discussion. The results suggest that anesthesiologists usually quickly detect abnormal values on physiologic monitors. Workload seems to influence anesthesia vigilance, evidenced by the effects of anesthetic phase and patient physical status. We plan to use this model to further investigate human and equipment factors which influence intraoperative vigilance.

S191

TITLE: **THE ROLE OF INTRATHECAL NEUROLYSIS IN THE TREATMENT OF CANCER-RELATED PERIANAL AND PERINEAL PAIN.**

AUTHORS: **J.Lynch, D.Zech, S.Grond.**

AFFIL.: **Dept. of Anaesthesia, Cologne University, Germany.**

Introduction: Intrathecal neurolysis (ITN) is claimed to provide excellent and prolonged pain relief for perianal pain in selected cases. However it is not a trivial procedure as urinary and faecal incontinence may occur. Although desireable,[1] detailed information on analgesic type and dosage or quantitative/qualitative assessment of pain before and after ITN to assess its risk/benefit ratio is rarely available. These points are addressed in the present study.

Methods: 9 patients (7m:2f) aged 49-77y (mean 63y) who had underwent surgery for rectal (n=7), bladder (n=1) and caecal cancer (n=1) were studied. All patients had severe bi-lateral perianal pain (67%) and of these 3 had additional pain radiating down the posterior surface of the thigh. Pain was present for 3-7 months (mean:4.6mo) before ITN. All patients received nonopioid analgesics (NOA) (dipyrone, diclofenac or flurbiprofen), and opioids (morphine (n=6), buprenorphine (n=1) and tramadol (weak opioid)(n=2)). ITN (n=12) was performed (L5/S1) using phenol 7.5% (mean: 0.46ml) in glycerine giving 0.1ml increments (range:0.3-1.0ml) over 20 min until pain was relieved. Pain was assessed before and after ITN with VAS(0-100) and a graded 6-point verbal rating scale (VRS) (1=no pain). A diagnostic blockade was performed 1-3d prior to ITN with hyperbaric bupivacaine 0.5% (range: 0.3-0.6 ml) until pain-free.

Results: The mean dose of morphine decreased from 180 mg/d (range 55-520 mg/d) at the time of ITN to 146 mg/d (range 0-520 mg/d) one week later. Opioids were discontinued in 2 patients for 4 weeks. The doses of NOA remained unchanged or underwent only minor change in 7 out of the 9 patients. The mean VAS and VRS decreased from 48 (range 30-70) and 3.7 (range 3-5) to a mean of 27 (range 0-60) and 2.5 (range 0-3) respectively at 7 days following blockade. The mean duration of pain relief was 17.8 days (range 0-84d). A permanent urinary catheter was required in two patients. Otherwise, no other neurological abnormalities were observed before or after ITN.

Discussion: The goal of ITN in cancer-related pain is to provide long-lasting analgesia with a minimum of serious side-effects. Neither of these aims were acheived in our patients. We found a short duration of pain relief (17.8 days) and 2 patients had permanent urinary retention. Opioids could be stopped for 4 weeks only in two patients and the mean morphine dose was reduced by only 20% in the remaining patients. Conventional analgesic pain treatment based on WHO-guidelines remains of paramount importance in the treatment of cancer-related perianal pain, as does the prior utilization of other lower risk techniques before considering the use of ITN.

References: 1. Pain 1990: 41; 267

S192

TITLE: EFFICACY OF ELECTROCONVULSIVE THERAPY (ECT) AFTER PROPOFOL (P) OR METHOHEXITAL (M) ANESTHESIA

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INTRODUCTION: One of the unsolved questions of electroconvulsive therapy (ECT) is the effect of seizure duration on the efficacy of treatment[1,2]. P, a recently introduced intravenous anesthetic was shown to shorten seizure duration during ECT[3,4,5,6] The question was raised whether the shortened seizure would adversely affect patients recovery from depression. This study was designed to compare the effect of seizure duration of two anesthetics, M and P on the efficacy of ECT.

METHODS: The study was approved by the IRB. 25 patients signed an informed consent. Only patients with the diagnosis of major depression were accepted for the study. A history, physical exam, lab results, EKG and a Hamilton Depression Scale (minimum score 18) were obtained prior to the first treatment. Patients were randomly assigned to receive either M or P as anesthetic for their complete set of 6 to 12 treatments. Both EEG and physical seizure duration was measured. M 0.75 mg/kg or P 1.0 mg/kg were given intravenously. The psychiatrists were blinded to the drug. Regression analysis was used for statistical significance.

RESULTS: 14 patients received M, 11 P. As expected there was a significant difference in mean EEG and physical seizure duration between the two groups. Hamilton score was slightly higher pre ECT in the M group, but the final score was identical regardless of anesthetic. (Table I) Both groups recovered at the same rate in spite of the shorter seizure times with P. The total number of treatments was 8.4 for M and 8.0 for P.

DISCUSSION: Our study supports previous reports that seizure duration does not influence recovery from depression.[1,2,7] Somewhat surprising and most impressive was the fact that all patients completed their ECT series with exactly the same Hamilton score.

Table I

	Methohexital N = 14	Propofol N = 11	p-value
Phys. Seiz.(sec)	36.7 ± 0.9	30.5 ± 1.2	<0.001
EEG Seiz. (sec)	65.0 ± 2.2	52.9 ± 2.5	<0.004
Hamilton Pre ECT	30.0 ± 2.1	27.4 ± 1.9	N.S.
Score Post ECT	6.6 ± 0.9	6.6 ± 0.8	N.S.
# Treatments	8.4 ± 1.3	8.0 ± 0.9	N.S.

REFERENCES: 1. Arch Gen Psychiatry 44:35, 1987; 2. J Nerv Ment Dis 135:237, 1962; 3. Br J Anaesth 59:1323, 1987; 4. Anaesthesia 43: 459, 1988; 5. Anaesthesia 45:623, 1990; 6. Anesthesiology 70:412, 1989; 7. Am J Psychiatry 142:692, 1987

S193

Title: THE EFFECTS OF EPIDURAL BUPIVACAINE COMBINED WITH FENTANYL OR SUFENTANIL ON FETAL HEART RATE

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Fentanyl and sufentanil have been added to epidural bupivacaine in order to improve the quality and duration of analgesia during labor. Recently it was observed that both 75mcg fentanyl and 5ml normal saline administered to 40 parturients with preexisting lidocaine epidural blocks produced a small but statistically significant decrease in both baseline FHR and variability. However, this study was limited to a small number of parturients, and utilized a larger dose of narcotics than that commonly employed for labor analgesia. We therefore decided to investigate this phenomenon further.

We have studied 318 ASA class I or II near-term parturients who had elected epidural analgesia for labor and vaginal delivery. After adequate hydration, an epidural catheter was placed at the second or third lumbar interspace, and all patients received a randomly allocated epidural regimen, selected as the minimal amount of bupivacaine and narcotic that reliably produced good analgesia in our patient population.

Group 1-a loading dose of 10ml of .125% bupivacaine with .5mcg/ml sufentanil, followed by a constant epidural infusion of .0625% bupivacaine with 0.3mcg/ml sufentanil.

Group 2-a loading dose of 10ml of .25% bupivacaine with 5mcg/ml fentanyl followed by a constant epidural infusion of 1mcg/ml fentanyl.

Maternal heart rate (MHR), maternal blood pressure (MBP), and baseline FHR were recorded at 5 minute intervals for 45 minutes prior to the administration of the initial epidural bolus and at 5 minute intervals after the injection for 90 minutes. Any decline in maternal systolic blood pressure below 100mmHg was treated with 5-10mg ephedrine IV. Any change in fetal heart rate variability during the study period was noted, and 1 and minute Apgar scores were recorded. The data were analyzed using analysis of variance for numeric data and contingency table analysis for categorical data.

Of the 318 patients, 151 received bupivacaine-fentanyl, and 167 received bupivacaine-sufentanil. The results are seen in table 1. Significantly fewer patients who received .125% bupivacaine with sufentanil experienced hypotension, compared with those who received .25% bupivacaine with fentanyl. We found significant decreases in maternal heart rate from pre-epidural levels in both dosage groups. No significant change in either baseline FHR or variability was found in either group. The number of 1 and 4 minute Apgar scores less than 6 did not differ between groups. Patients receiving .125% bupivacaine with sufentanil received significantly less local anesthetic than those receiving .25% bupivacaine-fentanyl.

Our data suggest that lower concentrations and doses of local anesthetic are associated with greater hemodynamic stability in parturients, but that neither dosage regimen significantly effected fetal heart rate, variability, or Apgar scores.

Table 1

	Control	.25% bup/fent	.125% bup/suf*
# SBP<100	14/318 (4.4%)	38/151 (25.1%)	13/167 (7.2%)*
tot. local (mg)	N/A	54.5 ± 12.6	31.3 ± 8.7*
MHR (bpm)	99.1 ± 9.1	87.5 ± 7.5	85.4 ± 6.9*
#Apgar<6	N/A	9/151 (5.9%)	4/167 (2.3%)
# FHR>5 bpm	14/318 (4.4%)	5/151 (3.3%)	7/167 (4.2%)
# variability	22/318 (6.9%)	11/151 (7.2%)	13/167 (7.7%)

* = $p < .02$, compared to control

S194

Title: AN OVERVIEW AND META-ANALYSIS OF HEPATOXICITY AFTER SINGLE EXPOSURE TO HALOTHANE

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Introduction: Mild postoperative jaundice or subclinical enzyme elevations after single exposure to halothane has been often attributed to that agent. This report reappraises mild hepatotoxicity following single exposure to halothane, using meta-analytic techniques for combining results from the most methodologically rigorous studies.

Methods: Study identification: A computerized search was performed of MEDLINE, and other databases of published abstracts and federally sponsored research for comparative clinical trials of halothane. Through the reference list of review articles and citation from primary studies, the search was extended back to 1958. **Exclusion criteria**: Studies including patients with previous exposure to halothane within 6 months or blood transfusions intraoperatively or in the previous 6 months were excluded. **Inclusion criteria**: Target population: clinical trials in adults and children. Design: controlled trials, randomized (RCT) or not (NRCT). Subjects: patients with no previous liver ailment and a normal baseline SGPT and other liver tests. Intervention: single exposure to halothane compared to other anesthetics. Measurement: liver enzymes assays including SGPT (ALT), SOCT or other enzymes used concurrently with SGPT. Statistical Analysis: Studies were selected in which frequency of enzyme elevations above the upper limits of normal were reported or analyzed. Odds Ratio (OR) estimates, an index of the extent of risk, with 95% confidence intervals (CI) were calculated when not reported. Meta-Analysis: Stratified analysis according to three sites of surgical procedures upper-, lower- and extraabdominal was performed. For studies meeting our eligibility criteria, pooling of results for all halothane groups compared with other anesthetics was done with the Mantel-Haenszel (MH) statistic yielding a summary OR with 95% CI about the overall incidence of hepatitis. A test for homogeneity was used to validate the use of MH statistic.

Results: Of 38 clinical trials identified, only 9 studies met our inclusion criteria (7 NRCTs and 2 RCTs). Stratification according to 3 surgery sites yielded comparatively higher OR for all anesthetics between sites: OR 8.1 and 7.9 when upper abdominal were compared to lower and extra-abdominal operations respectively, establishing site of surgery as the major confounder. OR was not statistically significant comparing halothane with other anesthetics for surgery at the same site. Pooled Analysis: A summary OR of 1.05 with 95% CI (0.83-1.31) and p=0.65 was obtained, indicating that halothane was not responsible for mild postoperative hepatitis reported. A 21% overall rate of abnormal enzymes with a total sample size of 1183 was obtained.

Discussion: Meta-analysis applies statistical principles to combining results from different studies. Our results suggest that: 1) single anesthetic exposure with halothane is not associated with hepatoxicity, 2) upper abdominal operations are associated with a higher risk (OR) of enzyme elevations than lower- or extraabdominal surgical operations, 3) pooling of these 9 studies yielded a 73% power, that is, the certainty with which a 25% increase in risk could be missed.

S195

Title: CRITICAL APPRAISAL OF METHODOLOGICAL REPORTING IN THE ANAESTHESIA LITERATURE

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Introduction: Adequate reporting of design and analytic issues is crucial to enabling readers to critically appraise results from articles. This would facilitate detection of articles worthy of attention. We have assessed and compared the extent of methodological reporting in 5 peer-reviewed anesthesia journals.

Methods: Eligible clinical trials defined as prospective, comparative evaluations of an intervention in humans were identified following a review by 2 authors, of all the 1989 issues of 5 journals (see table) selected on the basis of their citation ranking. After stratification by journals and issue throughout 1989, 100 randomly selected articles were divided randomly in 2 groups of 50, and read twice by 2 readers. All articles were scored as the sum of presence (1) or absence (0) according to 10 criteria: 1) subject eligibility criteria, 2) method of allocation, 3) description of the allocation method, 4) subjects' blindness to intervention, 5) blind assessment of outcome, 6) adverse effects, 7) loss to follow-up, 8) statistical analysis, 9) statistical methods, and 10) power/size calculations. **Statistical considerations**. A power of 90% was selected permitting detection of a "clinically" important absolute difference of 20% between journal mean scores with a sample size of 20 articles per journal. A two-tailed α of 0.05 was considered significant and the kappa statistic measured inter- and intra-rater agreement.

Results: Mean (SD) scores, based on 100 articles from 5 journals, were 6.5 (1.3) out of 10 (see table). A one-way ANOVA comparing the 5 means did not reach statistical significance (p=0.08). Two items, power/sample size and description of the method of allocation (e.g., technique of randomi-zation) with 2% and 21% respectively, were poorly reported. In contrast, eligibility criteria, method of allocation, use of statistical analysis and methods were adequately reported in more than 85% of articles. The 4 remaining criteria were reported inconsistently .

Discussion: An average of 65% of items reported compare favorably with 59% and 56% reporting from surgical and medical journals respectively.[1,2] However, 4 or more of our criteria need improved reporting. Concerns about reporting of important methodological aspects of clinical trials in anesthesia, while clarifying their applicability for the practitioner, should positively impact on the effective dissemination and acceptance of validated advances in anaesthesia practice.[3]

Scores for Five Journals

Journal	n	Mean, SD	95% CI
Annales Anes Francaise	20	7.2, 1.5	6.5-7.9
Can J Anaesth	20	6.5, 1.2	5.9-7.1
Br J Anaesth	20	6.4, 1.6	6.1-6.8
Anesthesiology	20	6.3, 1.1	5.7-6.8
Anesth Analg	20	6.1, 1.6	5.3-6.9
Total	100	6.5, 1.3	

References: 1.Surgery 95:572-80, 1984. 2.NEJM 306:1332-37, 1982. 3.Ann Int Med 113:724-28, 1990.

S196

TITLE: SARCOPLASMIC RETICULUM DYSFUNCTION DURING MYOCARDIAL STUNNING IN THE RABBIT HEART

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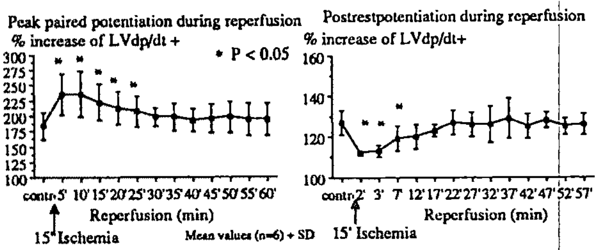
To investigate the mechanisms underlying the contractile dysfunction during myocardial 'stunning', potentiated state contractions were studied in a Langendorff rabbit heart model.
After isolation, a balloon was placed in the left ventricle to obtain isovolumetric contractions. After performing an AV-conduction block, the hearts were paced at a contant rate of 150 beats per minute. The potentiated state contractions (PSC) are elicited, either by paired-pulse stimulation (Peak Paired Potentiation: PPP) or by stimulation after 3 seconds of rest (Post Rest Potentiation: PRP.).
PPP reflects an increased influx of extracellular calcium during the second depolarization of the paired pulse, and increased loading of the intracellular calcium stores. In contrast, PRP may be attributed to functional redistribution of calcium from uptake site to release site within the Sarcoplasmic Reticulum (SR) during the rest period (2).
In six hearts the PPP and the PRP were determined in non ischemic conditions and after stunning of the myocardium (15' global ischemia followed by 60 minutes reperfusion). There was a transient decrease in LVdp/dt + of the PRP beat: 127±6% increase pre ischemia versus 113±3% post ischemia. (p<0.05). PPP however was well maintained: 184±22% preischemia versus 236± 34% postischemia.

After determining the PRP and PPP in control conditions another four hearts were exposed to a low dose of the irreversible SR blocker, Ryanodine (1*10-9Mol), during 40 minutes. The depression of the PRP after 10 minutes exposure was comparable to the depression, seen in the early reperfusion phase: % increase of LVdp/dt+ was 104±2% versus to 125±3% in control conditions. After 20' and 40' exposure the PRP was gradually reversed: the LVdp/dt+ of the first post rest beat was depressed to 65±5% and 47±7%respectively. The PPP was not depressed by Ryanodine: the % increase of dp/dt+ was 210%±5% after 40' compared to 181±13% during control conditions.
These results suggest that the transient depresssion of PRP in the stunned myocardium may be due to impairment of the SR function.



References:
1. Lukas A., R. Bose. Mechanisms of frequency-induced potentiation of contractions in isolated rat atria. Naunyn-Schmiedeberg's Arch Pharmacol 334:480-487,1986.

S197

TITLE: Perioperative Use of Transcranial Doppler in Patients with Head Injury

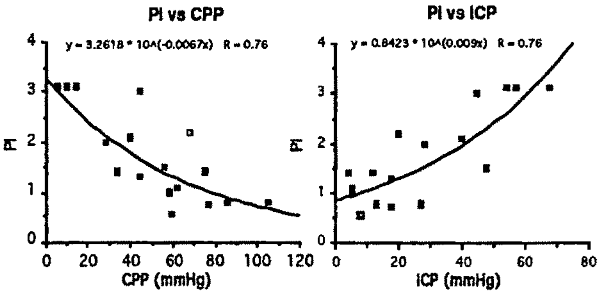
AUTHORS: T.A. Mayberg M.D., A. M. Lam M.D., F.R.C.P.C.

AFFILIATION: Departments of Anesthesiology and Neurosurgery, Univ.of Washington, Seattle, WA

Introduction: Transcranial Doppler ultrasonography (TCD) is a noninvasive monitor of intracerebral hemodynamics that was introduced into clinical practice recently. Although found to be useful for diagnostic purposes in a variety of clinical conditions, its perioperative use in patients with potentially increased intracranial pressure (ICP) has not been reported.

Method: After institutional approval, 17 consecutive patients (mean age 33, range 7-79 years) suffering from acute head trauma presenting to the operating room either for surgical evacuation of intracranial hematoma or extracranial surgical procedures were studied. There were 9 patients with closed head injury, 5 with subdural hematoma, 2 with ventricular hemorrhage and 1 with subarachnoid hemorrhage. TCD monitoring was performed with a Transpect transcranial Doppler (Medasonics) by insonating the right or left middle cerebral artery (MCA). Whenever there was a unilateral intracranial lesion, the ipsilateral MCA was insonated. Camino catheter for monitoring of ICP was either in-situ or placed perioperatively. TCD readings were taken either on arrival in the operating room, or at the time of placement of ICP monitor. Additional TCD readings were taken when there were changes in ICP. Other variables recorded included mean systemic blood pressure(MAP), cerebral perfusion pressure (CPP= MAP - ICP), heart rate, arterial CO_2 level (mean 29 mmHg, range 22-37 mmHg). Mean MCA velocity(V_{mca}) was calculated according to the following equation: V_{mca}= (systolic velocity - diastolic velocity)/3 + diastolic velocity. Flow resistance was assessed by calculation of pulsatility index (PI) where PI = systolic velocity - diastolic velocity/V_{mca}. PI - ICP and PI - CPP relationship were assessed using regression analysis. A p value of <0.05 was considered statistically signifcant.

Results and Discussion: Regression analysis of PI - CPP and PI - ICP yielded a significant exponential relationship (see figure). Although the R values were similar with both regressions, detailed examination of individual data suggest that PI was a better predictor of CPP than ICP; PI less than 1.3 was always associated with a reasonable CPP(> 50 mmHg) but may be associated with a high ICP. For prognostic purposes, PI > 2.5 and /or mean flow velocity < 20 cm/s was associated with poor patient outcome. The oscillating flow pattern(forward flow during systole and backward during diastole) was always associated with eventual death. Overall TCD monitoring was found to be therapeutically useful in 6/17 cases (intervention made based on TCD findings) and prognostically useful in 15/17 cases. We conclude that TCD monitoring may be useful in the perioperative care of patients with head injury, particularly in centers where ICP monitoring is not routinely used and more investigations are needed.



S198

TITLE: LOW DOSES OF ISOFLURANE/FENTANYL SUPPRESS SYMPATHETIC-ENDOCRINE RESPONSES TO NOXIOUS STIMULI IN CORONARY ARTERY BYPASS SURGERY

AUTHORS: T. Mayumi, Ph.D., S. Yokota, Ph.D., T. Yamamura, Ph.D., O. Kemmotsu, Ph.D.

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A recent report suggested that even large doses of fentanyl or sufentanyl could not produce and maintain complete surgical anesthesia. This study was undertaken to evaluate whether isoflurane (0.5 vol%) plus fentanyl (20-30 ug/kg) anesthesia could suppress sympathetic-endocrine responses to noxious stimuli during CABG and to compare with a high dose fentanyl (100 ug/kg) anesthesia.

Twenty four adult patients scheduled for elective CABG were studied after institutional approval and informed consent. The patients were randomly divided into two groups: group A: a single dose of fentanyl 100 ug/kg, group B: isoflurane 0.5 vol% plus fentanyl 20-30 ug/kg. Anesthesia was induced with intravenous midazolam and incremental doses of vecuronium were given to provide muscle relaxation in both groups. Hemodynamic variables(heart rate, blood pressure, cardiac output and pulmonary capillary wedge pressure)and hormonal concentrations (epinephrine, norepinephrine and cortisol) were determined before and after induction of anesthesia, and after intubation and after aortic cannulation.

The two groups were comparable for age, body weight and length, sex and ASA physical status. There were no differences in hemodynamic variables between two groups except an increased heart rate after aortic cannulation in group B. Hormonal concentrations were within normal limits and did not differ between groups (table).

The results indicate that isoflurane 0.5 vol% supplemented with a small dose of fentanyl could suppress sympathetic-endocrine responses to noxious stimuli in patients of CABG as could a high dose fentanyl. Isoflurane/fentanyl anesthesia is one of the suitable anesthetic methods for CABG which can produce and maintain satisfactory surgical anesthesia without deterioration of hemodynamics and hormonal concentrations.

Table. Hemodynamic variables and hormonal concentration in two groups.

			groupA		groupB	
Baseline	MAP	(mmHg)	84	± 5	83	± 7
	HR	(b.p.m.)	79	± 7	66	± 3
	C.O.	(l/min)	4.4	± 0.7	4.4	± 0.7
	Epi.	(ng/ml)	0.07	± 0.02	0.1	± 0.07
	Norepi.	(ng/ml)	0.24	± 0.05	0.2	± 0.03
	Cortisol	(μg/ml)	7.8	± 0.9	6.7	± 1.5
After induction	MAP		80	± 8	73	± 6
	HR		76	± 7	63	± 5
	C.O.		4.7	± 0.6	3.9	± 0.5
	Epi.		0.03	± 0.01	0.02	± 0.01
	Norepi.		0.21	± 0.04	0.2	± 0.03
	Cortisol		6.9	± 0.9	6.3	± 1.6
After intubation	MAP		76	± 6	70	± 7
	HR		72	± 6	80	± 7
	C.O.		4.7	± 0.5	4	± 0.7
	Epi.		0.03	± 0.01	0.02	± 0.01
	Norepi.		0.21	± 0.03	0.32	± 0.03
	Cortisol		6.3	± 1.2	6.2	± 1.3
After aortic cannulation	MAP		73	± 6	68	± 5
	HR		70	± 7	95	± 8*
	C.O.		3.8	± 0.4	3.5	± 0.4
	Epi.		0.03	± 0.01	0.05	± 0.02
	Norepi.		0.27	± 0.01	0.41	± 0.07
	Cortisol		6.4	± 1.4	7.9	± 2.2

Values are means ± SEM.
MAP: Mean arterial pressure, HR: Heart rate, C.O.: Cardiac output
Epi.: Plasma concentrations of epinephrine
Norepi.: Plasma concentrations of Norepinephrine
*: significantly different compared to group A

S199

Title: CEREBRAL PROTECTIVE EFFECTS OF NIMODIPINE IN PROLONGED HYPOTHERMIC CIRCULATORY ARREST IN DOGS

Authors: M.Mazzoni,M.D., C.K.Mezrow.M.S., H.Shiang,D.V.M., R.B.Griepp,M.D.
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Introduction: We previously reported studies in which two hours of circulatory arrest (CA) were associated with survival and minimal neurologic dysfunction. In part, the studies employed profound levels of hypothermia (10°C) and somatosensory evoked potential (SEP) monitoring to identify complete electrocerebral silence. Previous studies have demonstrated the protective effects of nimodipine, a dihydropyridine calcium antagonist in animal models of brain ischemia (1). The possibility of improving neurologic outcome with this agent following prolonged periods (3 hours) of hypothermic CA is the object of the present study.

Methods: Twelve mongrel dogs (20-25Kg) anesthetized with sodium pentobarbital were cooled to 10°C with combined surface/cardiopulmonary bypass (CPB), arrested for three hours, rewarmed and weaned from CPB.
Six animals were injected with a bolus dose of nimodipine (3ug/kg in 10 minutes) or saline (control) prior to circulatory arrest. At reperfusion nimodipine infusion (0.3mg/Kg/min) or saline (control) was initiated and continued for six hours. The dogs were evaluated daily for one week. During that period the extent of neurologic dysfunction was graded as follows: 1)Death within observation period, 2)comatose, 3)Holds head up, 4)Ataxic, 5)Normal.

Results: There were no deaths in the nimodipine treated animals and they manifested significantly less neurologic dysfunction following hypothermic CA compared to 100% mortality in the control group.($p<0.014$) (Fig 1).

Discussion: Nimodipine exerted demonstrable protective effects in this model of hypothermic ischemic brain damage. Combined hypothermic and pharmacologic protection may prolong the tolerable period of ischemia. It is of importance that the cerebral protective drug regimen can be initiated prior to the onset of the period of hypothermic CA.

References:

1. Nimodipine Improves Outcome when Given after Complete Cerebral Ischemia in Primates. Anesthesiology 62:406-414, 1985

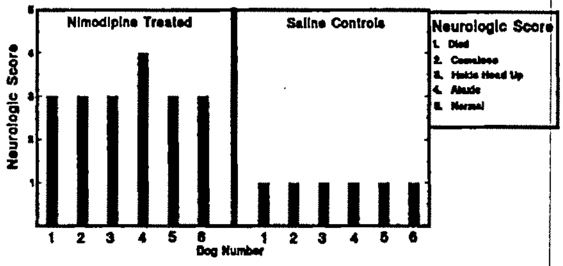

Figure: Mortality and neurologic dysfunction following three hours of hypothermic circulatory arrest: comparison of nimodipine and control groups.

S200

Title: ANALGESIC AND HEMODYNAMIC EFFECTS OF A 48-HR CONTINUOUS INTRATHECAL TIZANIDINE INFUSION IN DOGS

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Tizanidine(T) is an alpha-2 agonist which has been demonstrated to exhibit antionociceptive activity without hemodynamic alteration in rats after bolus intrathecal (IT) injections(1), with tolerance developing after repeated IT bolus administration similar to that exhibited with equianalgesic amounts of morphine. As part of our preclinical evaluation of T, this study was designed to evaluate the antinociceptive and hemodynamic effects of a continuous IT infusion in dogs.

Following IACUC approval, 6 mongrel dogs of either sex had an IT catheter placed at the L_{3-4} level through a laminectomy made at L_6. This catheter was connected to an injection port which was placed in a subcutaneous pocket. Another catheter was placed in the right carotid artery and connected to a similar port which was positioned on the back of the neck. After the animals were recovered from the initial surgery (1wk), analgesia was evaluated by placing the hind-paw over a slit in a platform and the time measured until withdrawal from a noxious stimulus (high intensity lamp) was measured. Control measurements were over a 6-hr IT saline infusion. Blood pressure was recorded continuously. Dogs were returned to the laboratory and the above protocol was repeated, this time with the dogs receiving a 1mg T bolus followed by a 250mcg/hr continuous infusion for 6 hrs. If adequate analgesia was maintained during the 6-hr infusion, the subcutaneous pocket was opened, and the injection port was replaced with an implantable osmotic pump designed to deliver 600mcg/hr. Animals were evaluated for analgesia over 48 hrs, afterwhich, they were sacrificed and their spinal cords removed for histology.

Analgesia as measured by foot withdrawal was maintained throughout the 6-hr infusion period. No changes in blood pressure or heart rate were observed throughout the study period.

Table 1: Percent Foot Withdrawal Inhibition

	1hr	6hrs	24hrs	48hrs
Saline control	8.9	12.1	2.8	8.8
6 hr infusion	81.0	72.2	----	----
48 hr infusion	----	----	61.0	61.0

These findings demonstrate the efficacy and lack of hemodynamic effect of a continual IT infusion of T. Further studies are underway utilizing higher infusions over longer time periods.

Reference: Pain 40:333-338, 1990.

S201

Title: EFFECTS OF PHENYLEPHRINE ON RIGHT VENTRICULAR PERFORMANCE IN PATIENTS WITH RIGHT CORONARY ARTERY DISEASE

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Right ventricular (RV) dysfunction associated with right coronary artery (RCA) disease may be exacerbated by decreases in RCA blood flow or increases in RV afterload. RV systolic and diastolic function could be effected by phenylephrine (PHE) in this manner, but has not been studied perioperatively. We sought to characterize has acute RV response to PHE required for systemic hypotension during induction of anesthesia for coronary artery surgery (CAS). After IRB approval, we studied 20 consenting adults with cardiac cath evidence of RCA disease, not receiving beta adrenergic blockers and requiring PHE administration during anesthetic induction. In addition to commonly monitored hemodynamic variables, RV ejection fraction (EF) was measured at end exhalation with a fast-response thermodilution pulmonary artery catheter (PAC). RV end diastolic volume (EDVI) and end systolic volume indices (ESVI) were calculated. Anesthetic induction consisted of sufentanil 7-10 mcg/kg, midazolam 50-100 mcg/kg and vecuronium. When declines in MAP prompted treatment, phenylephrine was infused until MAP increased 20% above baseline. Hemodynamic parameters were compared at baseline, during hypotension and after PHE, using ANOVA for repeated measures. Linear regression analysis was used to determine the relationship between RV volumes, EF and other hemodynamic variables.

After PHE, RVEF decreased in 7 patients (Group 1), and remained the same or increased in the remainder (Group 2). HR, MAP, PAOP, RAP, CI and stroke index (SI) did not differ between groups. Group 1 had a mean decline in RVEF of 13% from baseline and significant increases in RVESVI and RVEDVI. EDVI and ESVI were larger and RVEF was smaller at baseline in Group 1. Significant linear correlations were found between baseline RVEF and subsequent declines in RVEF (r=.62, p=.004), increases in ESVI (r=-.79, p=.001) and EDVI (r=-.75, p=.0001). No patient had ECG evidence of ischemia related to administration of PHE.

	GROUP	BASELINE	BEFORE PHE	AFTER PHE
RAP mmHg	1	11.9±2.1	10.5±1.9	13.1±1.6
	2	9.3±2.5	8.2±3.1	10.0±2.8
MAP mmHg	1	82.3±7.4	61.8±4.4	100.3±7.5$^{\int}$
	2	85.8±5.8	59.0±4.9	102.7±6.1$^{\int}$
RVEF	1	37.9±7.8	37.6±7.9	32.9±8.8$^{\int}$
	2	47.6±3.9*	45.1±3.3*	46.4±3.6*
SI ml/m^2	1	34.4±8.1	33.9±8.0	33.7±8.1
	2	34.7±4.6	35.2±5.1	34.7±4.5
RVEDVI ml/m^2	1	93.5±27.2	93.2±28.3	109.7±42.4$^{\int}$
	2	72.8±6.4*	77.9±8.4*	74.8±7.8*
RVESVI ml/m^2	1	59.1±25.3	59.3±25.5	75.9±41.1$^{\int}$
	2	38.1±4.1*	42.7±4.7*	40.1±5.0*

*intergroup difference; $^{\int}$difference from baseline; $p<0.05$

Although PHE infusion resulted in prompt correction of perfusion pressure without significant change in cardiac index, stroke index, or filling pressures, the volumetric PAC demonstrated significant alteration in RV performance in patients with RCA disease and low baseline RVEF. Importantly, RAP did not reflect changes in RVEDV. The changes in RV systolic and diastolic performance after PHE may be related to increases in RV afterload or decreases in RV intramyocardial blood flow despite increases in aortic perfusion pressure. These findings suggest that PHE should be used judiciously in patients with RCA disease and that volumetric PAC monitoring is useful for detecting abnormalities in RV performance not apparent with routine PAC monitoring.

S202

Title: ONDANSETRON, A SELECTIVE SEROTONIN TYPE 3 (5-HT$_3$) ANTAGONIST, REDUCES NAUSEA AND VOMITING IN FEMALES FOLLOWING MAJOR GYNECOLOGIC SURGERY

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Nausea and vomiting (N/V) continue to a major source of postoperative morbidity following major gynecologic surgery. Ondansetron (OND; GR38032F, Glaxo) a selective 5-HT$_3$ antagonist has previously been shown to effectively control chemotherapy-induced N/V. This multi-center study was designed to evaluate the prophylactic antiemetic efficacy and safety of OND in females undergoing major abdominal gynecologic surgery. IRB approved informed consents were obtained from 207 healthy (ASA I-II) subjects scheduled for elective inpatient gynecologic surgery. Unpremedicated patients were randomized to receive, in a double-blind manner, either OND 8 mg IV or placebo (PLA) infused over 2-5 min prior to general anesthesia induction, with a second dose infused 8 hr after the first dose. All patients received general balanced anesthesia. Postoperative pain relief was provided by meperidine or morphine. Hematologic, hepatic and renal parameters were evaluated prior to and 24 hr post study drug infusion. An antiemetic was given by the investigator under strict guidelines.

There were no significant differences in demographic data. The review of hospital records revealed protocol aberrancies in 25 of 107 OND patients and 19 of 100 PLA patients. These patients were excluded from efficacy calculations. Antiemetic efficacy is defined as complete response - no emetic episodes and no antiemetic administration for 24 hr after anesthesia. The complete response rate for OND (49/82; 60%) was significantly (p=<0.001) greater than PLA (21/81; 26%) for the 24 hr post-anesthesia period. Treatments were compared using the Mantel-Haenszel test.

Nausea was assessed on a numerical scale of 0 (no nausea) to 10 (worst nausea), at pretreatment, on awakening, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 24 hr. OND was significantly (p<0.001) better than PLA preventing nausea at all assesement times except on awakening. Treatments were compared using the Wilcoxon rank sum test.

No significant differences were found between groups with respect to study drug related adverse events. There were no significant study drug related changes in hematologic, hepatic or renal parameters 24 hr post treatment.

OND is a safe and effective antiemetic for the prophylactic control of N/V following major gynecologic surgery.

S203

Title: Influence of different pretreatment regimes on the neuromuscular effects of succinylcholine

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Introduction: Non-depolarizing muscle relaxants such as d-tubocurarine (T) are often used for the prevention of succinylcholine (S) myalgias. However these may interfere with the muscle relaxant effect of S[1]. Recently agents other than non-depolarazing relaxants have been suggested for the prevention of S pains[2]. The aim of the present study was to examine the influence of these pretreatment regimes on the neuromuscular blocking effects of S.

Patients and Methods: Fifty adult patients presenting for elective ophthalmic surgery were studied with their informed consent and ethical approval. Ten patient were each allocated to pretreatment with T 0.05 mg/kg iv 3 min before administration of S (group T), alphatocopherol 200 mg orally 6 hourly before operation for three doses (group A), chlorpromazine 0.1 mg/kg iv 3 min before administration of S (group Ch), soluble aspirin 600 mg orally 1 h preoperatively (group As), and a control group receiving saline (group C). They were anesthetized with fentanyl 3 µg/kg, thiopental 5 mg/kg and 66% nitrous oxide in oxygen and further increments of thiopental as required. The ulnar nerve was stimulated at the wrist with supramaximal stimuli of 0.2 ms duration in a train-of-four (TOF) mode and the adductor pollicis response recorded. After stabilization of the twitch response the iv pretreatment agent or saline was injected followed by S 0.5 mg/kg after a further 3 mins. The times taken to occurence of maximum block of the first reponse (T1) in TOF, and its reappearnace and return to 100% of control were recorded. The TOF ratio (T4/T1) prior to injection of S and any influence of the pretreatments on it was also recorded. The data were analysed using one-factor ANOVA, and Kruskal-Wallis and Mann-Whitney U tests. A p<0.05 was considered significant.

Results: Pretreatment with T was associated with a longer time to complete block with S (P<0.05). The reappearance of T1 occured in a significantly shorter time in this group (P<0.05) (table 1). Complete abolition of twitch response was achieved in all but 4 patients in group T and 1 patient each in groups A and Ch. Time to return of T1 to 100% was shorter in group T but the difference was not significant. Pretreatment with T was associated with significant fade in TOF prior to S(table 1), but in only one patient was a TOF ratio of <0.7 recorded. The onset and recovery times and TOF ratio were not significanly altered by the other pretreatment regimes.

Table 1 Neuromuscular effects of S in the presence of different pretreatments

	T	A	Ch	As	C
Onset (s)	71±25	53±14	49±9	53±13	49±11
Return of T1 (s)	172±67	307±60	301±80	254±61	296±97
Time to 100%T1(s)	420±115	607±123	549±76	551±77	532±208
TOF ratio before S	0.89	1.02	1.01	1.01	1.01

Discussion: The pretreatment regimes under study do not interfere with S blockade and may offer advantages over pretreatment with T.

References:

1. Freund FG, Rubin AP. Anesthesiology 1972; 36: 185-187.
2. McLoughlin C, Nesbitt GA, Howe JP. Anaesthesia 1988; 43: 465-467.

S204

Title: COMPARISON OF FIVE PRETREATMENT REGIMES FOR THE PREVENTION OF MUSCLE PAINS AND BIOCHEMICAL CHANGES AFTER SUCCINYLCHOLINE ADMINISTRATION

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Introduction: Occurence of muscle pains following succinylcholine administration is well known and this may be associated with an increase in serum creatine kinase (CK) levels[1]. Nondepolarising muscle relaxants are often used to reduce the incidence of these pains but may interfere with the neuromuscular blocking action of succinylcholine[2]. It has been suggested that the underlying mechanism of muscle damage following succinylcholine may involve phospholipid degradation with the release of damaging products of fatty acid metabolism[3]. The present study was designed to assess the effects of different pretreatments acting at the neuromuscular junction or on fatty acid metabolism on the severity of muscle pains and CK changes following succinylcholine.

Patients and methods: One hundred ASA grade I adult patients were included in the study with their informed consent and ethics committee approval. Twenty patients each were allocated to pretreatment with d-tubocurarine 0.05 mg/kg iv 3 min before induction (Group T), chlorpromazine 0.1 mg/kg iv 3 min before induction (Group Ch), alphatocopherol acetate 200 mg orally 6 hourly preoperatively for three doses (Group A), soluble aspirin 600 mg orally one hour before induction (Group As) or no pretreatment (Group C). Anesthesia was induced with thiopental 4-5 mg/kg followed by succinylcholine 1.5 mg/kg and tracheal intubation performed 1 min later. Maintenance of anesthesia was with 66% nitrous oxide in oxygen and isoflurane. No medication was administered by the intramuscular route for 24 hours postoperatively. Intubating conditions were assessed and graded as poor, adequate or good. Venous blood samples were withdrawn prior to induction of anesthesia and 1, 3, and 5 min and 24 hrs after succinylcholine for estimation of serum potassium (K') and CK levels. The presence of muscle pains at 24 hrs and 48 hrs was assessed by a blinded observer and these were graded as nil, slight, moderate or severe. Results were subjected to ANOVA, Kruskall-Wallis and Mann Whitney U tests.

Results: Muscle pains were significantly reduced in groups T, Ch and A (table 1). In addition CK rises were obtunded in groups T and Ch (mean±sem). Electrolyte changes were not significant in any groups.Intubating conditions were significantly worse in patients receiving tubocurarine pretreatment.

Table 1

	T	Ch	A	As	C
CK: 0	83±9.7	94±10.2	80±9.4	83±14.9	78±7.1
: 24h	79±9.5	107±14.9	117±14.4	167±38	171±32
myalgia(%)	15	15	10	20	55

References:

1. Tammisto T, Airaksinen M. British Journal of Anaesthesia 1966; 38: 510-515.
2. Erkola O, Salmenpera A, Kuoppamani R. Acta Anaesthesiologica Scandinavica 1983; 27:427-432.
3. McLoughlin C, Nesbitt GA, Howe JP. Anaesthesia 1988; 43: 565-567.

S205

Title: METOCLOPRAMIDE DECREASES THIOPENTAL HYPNOTIC REQUIREMENT
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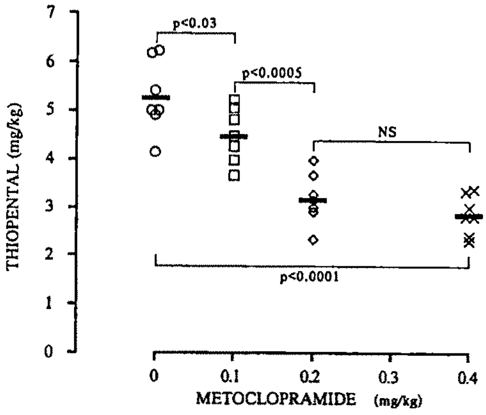
Metoclopramide (MCA) is a selective D2-receptor antagonist. It stimulates gastric emptying and has antiemetic properties. In contrast to droperidol, MCA when used for prevention of postoperative nausea and vomiting does not delay recovery from anesthesia (1). At the same time, MCA has a potential to facilitate hypnosis: when used in higher doses, it may produce drowsiness (2). The aim of the study was to determine whether MCA decreases thiopental requirement for induction of anesthesia.

Unpremedicated ASA physical status I or II adult female patients participated in this randomized, double blind, controlled study approved by the Institutional Human Investigation Committee. Thiopental requirements were determined in 4 groups of 7 patients: control (saline) and MCA 0.1, 0.2, and 0.4 mg/kg, i.v., administered 5 minutes before thiopental. Thiopental was given at a rate of 35 mg/min until the patient lost the ability to open eyes on command.

The thiopental requirements were 5.3 ± 0.3 mg/kg in the control group and 4.5 ± 0.2 mg/kg (Δ14%, $p<0.03$), 3.2 ± 0.2 mg/kg (Δ39%, $p<0.0001$), and 2.9 ± 0.2 mg/kg (Δ45%, $p<0.0001$) in the MCA 0.1, MCA 0.2, and MCA 0.4 groups, respectively (figure).

The results indicate that MCA decreases thiopental hypnotic requirement in a dose-dependent fashion. This effect is probably associated with the blockade of the central dopamine receptors. When MCA is given, in the recommended doses of 10-20 mg per patient, the induction dose of thiopental may be reduced by 1/4 to 1/3.

References:
1. Anesthesiology 60:67, 1984
2. Drugs 25:451, 1983



S206

Title: COMPARISON OF RAPID INTUBATING CONDITIONS WITH THIOPENTAL VS. PROPOFOL, SUCCINYLCHOLINE VS. TIMING TECHNIQUE WITH ATRACURIUM
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Recently the "timing principle" has been advocated for rapidly intubating adults where vecuronium is administered before the I.V. induction agent and intubation carried out within two minutes.[1] In this study, the conditions for intubation and the cardiovascular responses were evaluated in adults induced with Thiopental (T) or Propofol (P) and Succinylcholine (S) the usual way, or Atracurium (A) with the timing technique.

Methods: Forty consenting ASA I & II adults, premedicated with 1 - 2 mg midazolam were studied in four randomly allocated groups.

I: T, 5 mg/kg IV. 1 min later, S, 1 mg/kg.
II: P, 2.5 mg/kg. 1 min, S, 1 mg/kg.
III: A, 0.5 mg/kg. 20 sec, T, 5 mg/kg slowly in 60 sec.
IV: A, 0.5 mg/kg. 20 sec, P, 2.5 mg/kg slowly in 60 sec.

In all patients, endotracheal intubation was attempted two min after the administration of the first drug. Blood pressure and pulse rate were recorded by Dinamap^{R}, pre-induction, 30 sec after each drug and for three min after intubation. Intubating conditions were classified as: excellent: complete relaxation of all muscles; satisfactory: cords midway, slight coughing after intubation; and poor: cords adducted, strong coughing. Data were analyzed using Student's t-test, ANOVA and chi square.

Results: In all groups, a significant rise of BP ($P < 0.01$) was noted after intubation. It was more marked in patients receiving T & S (Group I, 45% increase), than in the other 3 groups (30%). No significant changes were seen in the heart rate. The rise of BP was more pronounced in patients receiving T than P ($P < 0.05$).

Intubating conditions:

	Excellent	Satisfactory	Poor
Group I	5	5	0
Group II	6	3	1
Group III	4	6	0
Group IV*	9	1	0

* $P < 0.02$ compared to other 3 groups.

Discussion: The timing technique for endotracheal intubation with A & P provided better conditions of intubation compared to standard T/P & S or A & T with priming technique, probably because intubation is performed during the peak effect of propofol. Thiopental seems to lack this effect. The advantage of timing technique with a muscle relaxant is that the use of large doses of propofol are avoided that cause hypotension.

References:
1. Anesthesiology 73:244-248, 1990.

S207

Title: MILD HYPERTHERMIA AND THE HUMAN PUPILLARY LIGHT REFLEX

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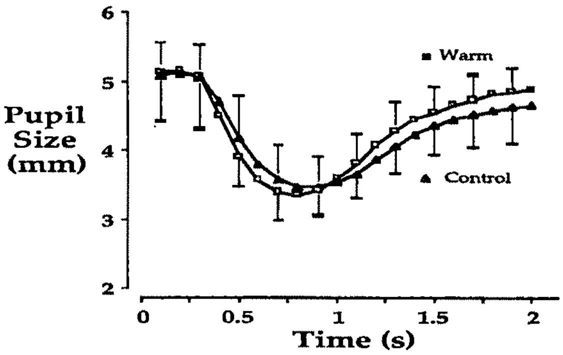
The pupillary light reflex is often evaluated as a measure of midbrain function or anesthetic level. We recently demonstrated that mild central hypothermia does not significantly decrease the light reflex.[1] Because many patients recovering from neurosurgery are febrile, we tested the hypothesis that mild hyperthermia does not produce a clinically significant increase in the light reflex. A circulating water blanket and forced-air warmer (Bair Hugger®) were used to increase distal esophageal temperatures ≈2°C in six unanesthetized volunteers. Pupillary light reflexes were measured during the control period (36.5 ± 0.3°C) and at peak central temperature (38.2 ± 0.2°C) using a portable infrared pupillometer (Fairville Medical Optics, Inc). The reflex was elicited by a 0.5 sec light flash, and pupil size was recorded at 0.1 sec intervals starting immediately before the flash. Hyperthermia did not significantly alter pupil size or reflex amplitude. The maximum constriction velocity and maximum redilation velocity were increased slightly ($P<.05$) (Fig). Although statistically significant, the changes we observed were not clinically important and would not be apparent using a traditional pen light examination. We conclude that typical peri-anesthetic thermal perturbations are unlikely to confound pupillary responses.



Legend: Average pupillary light reflex in volunteers during the normothermic control period and at 38.2 ± 0.2°C. Hyperthermia did not produced clinically significant increases in the pupillary response.

Reference: 1) Anesthesiology 75:62-67, 1991.

Supported by NIH grant #R29 GM39723.

S208

Title: EFFICACY OF TRANSDERMAL FENTANYL FOR POSTOPERATIVE ANALGESIA IN CANCER PATIENTS

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Introduction: Fentanyl has been incorporated into a transdermal delivery system. We sought to determine the safety and efficacy of a skin patch containing a reservoir of fentanyl with a membrane that dispenses a consistent amount of the drug continuously controlling pain following laparotomy.

Methods: After Institutional Review Board approval and signed informed consent, ASA PS I and II female patients were randomly assigned to receive either a low dosage fentanyl (LDF) patch (70 to 80 µg/h), a high dosage fentanyl (HDF) patch (90 to 100 µg/h), or a placebo patch. One hour preoperatively, physically identical transdermal patches were placed on the upper chest. General anesthesia was induced with thiopental 2 to 3 mg/kg IV, fentanyl 1 to 5 µg/kg IV, and succinylcholine 1.5 mg/kg IV. Inhalation of 60% nitrous oxide, 0 to 1.3% isoflurane and oxygen maintained general anesthesia. Muscle relaxation was maintained with vecuronium, 0.05 mg/kg IV initially and 0.01 mg/kg IV subsequently. Postoperative pain control was supplemented with intravenous morphine sulfate (MS) administered with a patient-controlled analgesia technique. The loading dose of MS was 40 µg/kg, with a demand dose of 20 to 40 µg/kg with a ten-minute lockout. No maintenance morphine was given. Vital signs, arterial oxyhemoglobin saturation (SpO_2), and pain intensity (visual analog scale [VAS]) were recorded at 2-h intervals for the first 12 h, then at 4-h intervals for 24 h thereafter. Patches were removed 24 h after placement. Data are presented as mean ± SD. Statistical comparisons of intergroup data were made with an analysis of variance and Scheffé's *post hoc* test.

Results: Forty-one patients aged 52±13 years were studied. No significant differences in demographics, type or duration of operation, or use of intraoperative narcotics existed among the groups. The difference between the cumulative dosage of MS in the placebo patch group (47.4±26.6 mg) and in the LDF patch group (27.3±19.8 mg) was not statistically significant ($p=0.09$). However, the cumulative dosage of MS was significantly greater in patients who received the placebo patch (47.4±26.6 mg) than in those who received the HDF patch (23.5±23.0 mg) ($p=0.035$). No significant intergroup differences were noted in postoperative heart rate, blood pressure, VAS scores, sedation scores, or frequency of hypoxemia (SpO_2 <90%) at any time during the study.

Discussion: A reliable transdermal analgesic system could be useful in the treatment of postoperative pain. Transdermal fentanyl safely provided a continuous, uninterrupted source of active agent, without discomfort or expensive delivery equipment. In this study, transdermal fentanyl reduced the postoperative use of intravenous morphine sulfate and did not significantly increase the frequency of arterial blood desaturation. We conclude that transdermally delivered fentanyl is a safe and effective adjunct to postoperative pain management after laparotomy.

This study was supported by a Grant from Anaquest

S209

Title: TO BE OR NOT TO BE IN A CLINICAL TRIAL:
A SURVEY OF SURGICAL PATIENT'S ATTITUDES

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Introduction As more patients undergo surgery on a day of admission (DAS) or ambulatory (AMB) basis, it is important to recognize the special needs of this population so that clinical research can be conducted while maintaining the patient's autonomy and dignity.[1,2] The purpose of this study was to determine the factors that may influence the AMB or DAS patient's decision to participate in clinical anesthesia research.

Methods Following IRB approval and written informed consent, 74 AMB and DAS patients were asked to complete a survey upon admission on the day of their proposed surgery. Patients were approached in a setting identical to that in which they might be asked to participate in clinical anesthesia research. Questions were of the "Yes", "No", "Don't know" variety, and also offered responses to check off. Patients also scored their anxiety on a linear visual analog scale (VAS). Internal consistency between similar questions was assessed by chi-square analysis, confirming the validity of the survey.

Results 36 DAS and 38 AMB patients, mean age 43 years, participated. All patients completed at least 60% of the survey. 100% cited receiving best medical care as the major reason to participate in a protocol, 92% felt that contributing to scientific knowledge and helping society was important. Only 9% felt that medical research is unethical. We found no significant difference by age, gender, race, level of education or whether DAS or AMB as to whether a patient would consent to participate in a study. The mean VAS score for anxiety level of the DAS patients who would consent was significantly lower than that of DAS patients who would not. The VAS scores for the AMB patients showed no difference between those who would or would not consent to a study. Concerning acceptable circumstances for being approached for a study, 80% preferred having a family member present; 87% preferred consulting with their treating physician; 86% preferred being approached in a private office setting and while fully dressed (i.e. not in a hospital gown) Being first approached for a study in the OR holding area was unacceptable to most (93%).

Discussion Our results suggest that surgeon involvement in the proposed research may be essential, both to encourage patient participation and to provide adequate time for the patient to understand the protocol. This may be of particular importance in the AMB patient, since most of those responding considered it inappropriate to be approached on the day of surgery. For the DAS patient, surgeon involvement is desirable since the anesthesiologist making the preadmission interview may not be an investigator.

References 1) Anesth Analg 68:649-53, 1989.
2) Anesthesiology 67:A567, 1987.

S210

Title: COMPARISON OF THE INTUBATING CONDITIONS AND SOME NEUROMUSCULAR EFFECTS FOLLOWING ADMINISTRATION OF ORG 9426 AND SUCCINYLCHOLINE

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INTRODUCTION: Succinylcholine (Suc), because of its rapidity of action, is currently the only muscle relaxant suitable for facilitating rapid tracheal intubation. However it has many side effects and its use may be undesirable in certain circumstances. Atracurium and vecuronium while associated with an intermediate duration of action are relatively slow in onset of action unless used in relatively large doses. Org 9426 (Org), a desacetoxy derivative of vecuronium has been suggested as an agent which may have a rapid onset of action because of its relatively low potency[1]. In the present study we have compared the conditions for tracheal intubation following Suc and Org and assessed the onset and duration of clinical relaxation after administration of Org.

PATIENTS AND METHODS: Eighty adult patients of ASA class I or II scheduled for elective surgery requiring tracheal intubation were included in the study with their informed consent and ethical review. Following premedication with oral temazepam 20 mg anesthesia was induced with fentanyl 2-3 µg/kg and thiopental 3-5 mg/kg and maintained with 67% nitrous oxide in oxygen and further small doses of fentanyl and/or thiopental. Ventilation was adjusted to normocarbia. The ulnar nerve was stimulated with supramaximal stimuli of 0.2 ms duration at 0.1 Hz and the force of contraction of adductor pollicis recorded. Following stabilization of the control responses 40 patients each were randomly allocated to receive 0.6 mg/kg of Org or 1.0 mg/kg of Suc. Tracheal intubation was attempted at 60 or 90 s. The intubating conditions were assessed using the scheme of Lund and Stovner[2] and graded as excellent, good, fair or poor, the first two being considered clinically acceptable. The time taken to complete block of the twitch and its recovery to 25% (duration of clinical relaxation) after Org and to 90% after Suc were recorded.

RESULTS: The intubating conditions with the two relaxants are given in Table 1 and show these to be acceptable at both times in all patients given Suc and in 95 and 100% of patients given Org. The time to complete block was 60±8.4 s (SD) after Suc and 89±12.3 s after Org. The time to 25% recovery of twitch was 30.5±5.1 min after Org and to 90% recovery after Suc was 13.3±3.1 min. There was no evidence of histamine liberation or other significant side effects.

Table 1: Intubating conditions after Org and Suc

	Org 60 s	Org 90 s	Suc 60 s	Suc 90 s
n	20	20	20	20
Excellent	13	17	19	20
Good	6	3	1	0
Fair	1	0	0	0

DISCUSSION: Org appears to be a drug with a more rapid onset of effect than other nondepolarizing agents currently available or under investigation with a duration of action resembling that of atracurium and vecuronium. The intubating conditions after 0.6 mg/kg (2xED95) are good to excellent at 60-90 s. The agent may be used in higher doses to facilitate even earlier intubation as there are few side effects.

REFERENCES:
1. Bowman WC, Rodger IW, Houston J et al. Anesthesiology 1988; 69:57-62.
2. Lund I, Stovner J. Acta Anaesthesiol Scand 1962; 6: 85-97.

S211

TITLE: ANALGESIC EFFECT OF EPIDURAL SUFENTANIL AND CLONIDINE IN COMBINED USE

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Epidural (Ep) sufentanil has been shown to produce potent analgesia of relatively short duration.[1] Clonidine, an $alpha_2$ - adrenoreceptor agonist has been reported to provide effective analgesia by epidural administration.[2] The present study was undertaken to evaluate the synergistic interaction of Ep administration of sufentanil and clonidine.

After giving their consents, 45 adult patients scheduled for abdominal surgeries were enrolled in this study. Prior to anesthesia induction indwelling lumbar epidural catheters were placed in all patients who then received general anesthesia with inhalation anesthetic and without narcotic analgesics. In the postoperative period, when the patients first complained of pain, they were divided into 3 equal groups of 15 patients each in a randomized and double blinded fashion with group I receiving Ep sufentanil 10 mcg; group II receiving Ep clonidine 150 mcg; and group III receiving Ep sufentanil 10 mcg plus clonidine 150 mcg. All patients were observed for pain relief, sedation, vital signs, arterial blood gas studies and adverse effects for 24 hours.

Onset of pain relief with Ep sufentanil was rapid at 5 minutes and peaked at 20-30 minutes with a duration of action lasting about 4 hours. Ep clonidine showed a slower onset of analgesia at 10 minutes and peaked at 45-60 minutes with a duration of action about 7 hours. The combination of sufentanil and clonidine had a fast onset, same as that of sufentanil alone, and a duration same as that of clonidine. The combination group also showed an additive incidence of adverse effects which included nausea, vomiting, sedation, hypotension, bradycardia and reduction of respiratory rate. However, no clinically significant respiratory depression was observed in any of the patients.

Our study showed that combined administration of epidural sufentanil and clonidine produced analgesic effect similar to that of Ep clonidine alone but with additive adverse effects. This combination does not seem to offer any advantage for clinical use.

References

1. Anesthesiology 68(3):448-454, 1988.
2. Acta Anesthesiol. Scand. 32:702-709, 1988.

S212

TITLE: Desmopressin Decreases Blood Loss and Transfusion Therapy after CABG with Prolonged Bypass Times

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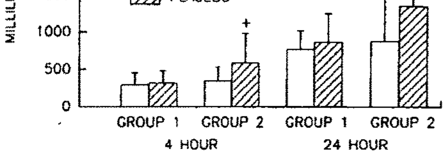
Post cardiopulmonary bypass (CPB) bleeding is a complication which may be altered by administration of desmopressin (DDAVP). The purpose of this study was to determine the effect of DDAVP on post coronary artery bypass grafting (CABG) blood loss and transfusion therapy in patients with normal and abnormal platelet function as indicated by the maximal amplitude (MA) of the thromboelastogram.
Methods: After obtaining institutional approval and written informed consent, 115 patients were prospectively evaluated in a randomly assigned, double blind, placebo controlled trial. Hematocrit, platelet count, prothrombin time, partial thromboplastin time, thrombin time, fibrinogen, and a native whole blood thromboelastogram (TEG) were measured preoperatively, after protamine titration and upon arrival in the intensive care unit. After protamine titration, desmopressin (0.3 μ/kg) diluted in normal saline or normal saline was administered. Postoperative mediastinal chest tube drainage and transfusion therapy were recorded.
Results: Patients were divided into 2 groups based upon a TEG MA > 50mm, (normal) or < 50mm (abnormal). Those groups were further divided into DDAVP and placebo treated subgroups (Gr 1: DDAVP 44, Placebo 42; Gr 2: DDAVP 13, Placebo 16) Demographic, surgical and anti-anginal therapy was similar except for patient size (BSA: Gr 1, 2.0±0.2; Gr2, 1.8±0.2, $p< 0.05$). CPB times were equivalent (129.7±33.8 vs 134.2±39.3 min). Post-CPB differences between Gr 1 and 2 were a significantly smaller alpha angle (47.5±9.2 vs 38.2±8.4) and MA (54.2±7.3 vs 39.4±5.6 mm). Those abnormalities persisted in the final TEG assay. The effect of DDAVP on mediastinal chest tube drainage is shown in Fig. 1. Fewer DDAVP treated patients in both groups received blood products ($p< 0.05$). A reduction in number of units transfused was observed in the DDAVP patients in Gr 1 ($p< 0.05$).
Discussion: DDAVP administration was efficacious in reducing blood loss when the TEG was abnormal after CPB. The number of units transfused and number of patients exposed to blood products was also reduced by DDAVP administration. In patients undergoing CABG with a prolonged CPB time the administration of desmopressin may be beneficial in reducing blood loss and transfusion therapy.



S213

TITLE: **ANALGESIC EFFICACY OF EMLA DURING OUTPATIENT SHOCK-WAVE LITHOTRIPSY**

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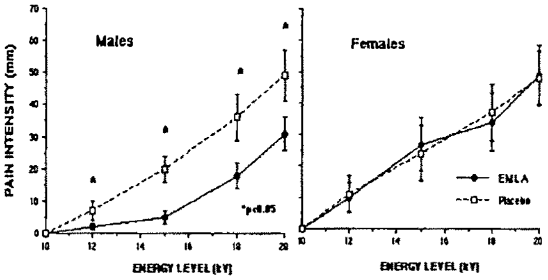
EMLA (Eutectic Mixture of Local Anesthetics) is a novel local anesthetic cream containing a mixture of lidocaine and prilocaine. Previous studies have reported that EMLA can penetrate intact skin and provide dermal analgesia for superficial surgical procedures.[1,2] We designed a randomized, double-blind study to assess the efficacy of EMLA in minimizing pain associated with shock waves generated during lithotripsy procedures.

58 consenting ASA I-III adult outpatients scheduled to undergo immersion lithotripsy with the Dornier HM3 lithotriptor were randomly assigned to one of two treatment groups according to an IRB-approved protocol. All patients had the study medication applied to a 10x20 cm area overlaying the kidney to be treated. Cream for the treatment group (E,n=30) contained 30 g of EMLA, while the placebo group (P,n=28) received an equal amount of the cream. The cream was left undisturbed under an occlusive dressing for 90 min. Following premedication with midazolam, 2 mg iv, the patients were positioned in the lithotriptor and monitors were applied to measure mean blood pressure, heart rate, respiratory rate, and oxygen saturation. Following five test shocks at 10, 12, 15, 18 and 20 kV, patients were asked to evaluate the pain intensity using visual analog scores (VAS) with 0 = none to 100 = maximum. If the patient complained of severe pain or reported a VAS greater than 70, test shocks were discontinued. Data were analyzed using ANOVA with repeated measures and Chi-square tests, with $p<0.05$ considered significant.

The two study groups were comparable demographically [age: 53±12(E) vs 50±12(P) yr; weight: 80±19(E) vs 82±19(P) kg; male: 63%(E) vs 67%(P)]. Overall, pain scores were significantly lower in the EMLA (vs placebo) group for test shocks at 15, 18 and 20 kV. However, EMLA cream was significantly more effective in male than female patients (figure). Hemodynamic responses were comparable between the two groups at all energy levels (kV).

In conclusion, EMLA significantly decreased pain produced by test shocks >15 kV. Possible explanations for the decreased efficacy of EMLA cream in females include differences in pain perception, skin thickness, and/or dermal penetration. Further studies are needed to evaluate the causes of the gender-related differences in the response to EMLA cream during lithotripsy.

References: 1. Anesth Analg 67:115-123, 1988
2. Br J Anaesth 64:173-177, 1990



S214

Title: EFFECT OF BARBITURATE ON HEPATIC CIRCULATION AND OXYGEN METABOLISM DURING HYPOXIA IN DOGS

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Introduction: Depression of hepatic circulation and/or hepatic oxygen metabolism during anesthesia could be a cause of post anesthetic hepatic injury. The present study was designed to determine whether thiamylal could maintain hepatic circulation and oxygen metabolism even in the presence of hypoxia compared with halothane.

Methods: Hepatic oxygen delivery, consumption and the hepatic energy charge were assessed in twenty-one mongrel dogs receiving 1 to 1.5 MAC of halothane or thiamylal (20-30 $mg \cdot kg^{-1} \cdot h^{-1}$) intravenously while inhaling graded hypoxic mixtures (FIO_2 0.21 to 0.08). Hepatic blood flow was measured using electromagnetic flowmetry: hepatic oxygen delivery and consumption were calculated from hepatic blood flow and oxygen content in hepatic arterial, portal venous and hepatic venous blood.

Results: In the hypoxia-halothane group, portal venous blood flow (FIO_2 0.15-0.10), portal venous oxygen content (FIO_2 0.10-0.08) and hepatic oxygen consumption (FIO_2 0.08) significantly decreased compared with the hypoxia-thiamylal group. Arterial ketone body ratio (AKBR), which indicates the mitochondrial energy charge level, decreased with the development of hypoxia, and in the hypoxia-halothane group, the decrease of AKBR was significantly greater than in the hypoxia-thiamylal group at FIO_2 0.08. The serum catecholamine levels, epinephrine and norepinephrine, increased in both groups at FIO_2 0.08. In the hypoxia-halothane group, however, the increase of norepinephrine was significantly higher than in the hypoxia-thiamylal group at FIO_2 0.08.

Discussion: It was reported that thiopental or volatile anesthetics might inhibit oxygen metabolism under hypoxic condition *in vitro* (1). However, results in the present study suggest that, compared with halothane, thiamylal could suppress the exaggerated reaction to hypoxic hypoxemia, maintain hepatic circulation and hepatic oxygen metabolism and therefore maintain the hepatic mitochondrial redox state in better condition.

Reference : (1) Becker, G.L. Anesth Analg 67: 923-928, 1988.

S215

TITLE: COGNITIVE AND NEUROLOGICAL FUNCTION AFTER CORONARY ARTERY SURGERY: A PROSPECTIVE STUDY

AUTHORS: JM Murkin MD, FRCPC; JS Martzke, PhD; AM Buchan MD, FRCPC; DS Sharma, RN; PL Campbell, RN. **AFFILIATION:** Departments of Anaesthesia, Psychology, and Clinical Neurological Sciences, University Hospital, University of Western Ontario, London, Ontario. Supported by OHF Grant #A1498.

The current study was designed as part of a prospective assessment of neurological and psychometric outcomes after cardiopulmonary bypass in patients undergoing elective coronary artery bypass (CAB) surgery, and represents data obtained within the first 24 months of the study. METHODS: After obtaining institutional approval and written informed consent, 245 patients (86% males, mean age = 60.6 years, mean education = grade 11) undergoing elective CAB using hypothermic cardiopulmonary bypass were assessed pre-operatively (baseline), 7 days post-operatively, and at 8 week follow-up. The neurologic exam employed was a structured, quantifiable bedside exam assessing neurologic functions on a scale of 0 to 3 in each of 15 areas. Areas assessed included domains of mentation, cranial nerves, motor and sensory functioning, cerebellar functioning and gait, and reflexes. The neuropsychologic screen was comprised of 1) the Digit Span and Mental Control subtests of the WMS ("concentration"), 2) the Digit Symbol subtest of the WAIS-R ("psychomotor speed"), 3) the Grooved Pegboard test ("dexterity"), and 4) the Verbal Paired Associates subtest of the WMS ("verbal learning"). Alternate forms of the Digit Span, Mental Control, and Verbal Paired Associates were employed and administered in an ABA sequence for half the patients, and a BAB sequence for the other half, so as to reduce practice effects across the first two assessments. Subjects served as their own controls since post-operative scores (7 day and 8 week follow-up) were contrasted with pre-operative baseline scores. Criterion for defining deterioration on the neurologic exam was a drop of 2 or more points (which required either a marked decrease in one area, or two distinct, modest decreases), whereas within each cognitive domain, a group standard deviation was computed at baseline and deterioration defined as a drop in performance greater than the baseline standard deviation for that domain. RESULTS: At 7 days, cognitive and neurologic scores had declined for 56% and 38% of patients, respectively. Percentages declined within each cognitive domain were as follows: concentration = 18%, psychomotor speed = 15%, dexterity = 24%, and verbal learning = 29%. The combined frequency of decline at seven days (i.e., neurologic or cognitive decline) was 67%. At 8 week follow-up, cognitive and neurologic scores were declined from baseline for 18% and 22% of patients, respectively. The combined frequency of decline (neurologic or cognitive) was 33%. The distribution of cognitive decline at follow-up within each domain was as follows: concentration = 6%, psychomotor speed = 5%, dexterity = 4%, and verbal learning = 8%. DISCUSSION: A comparison of the rates of decrease in morbidity (cognitive versus neurologic) from the 7 day to the 8 week examinations suggests cognitive deficits are more likely to be transient, while neurologic deficits are more likely to be chronic. This suggests both cognitive and neurologic measures contributed uniquely to morbidity estimates and underscores the need to employ both measures in studies exploring the efficacy of procedures designed to reduce morbidity.

S216

Title: PERIOPERATIVE STIMULATION OF CYTOKINE PRODUCTION IS IMPORTANT IN THE STRESS RESPONSE OF H-P-A AXIS

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It is well-known that surgical invasion stimulate the hypothalamo-pituitary-adrenal (H-P-A) axis and induce marked elevation in both plasma levels of adrenocorticotropic hormone (ACTH) and cortisol. It has been suggested recently that some classes of cytokine are involved in the activation of H-P-A axis associated with upper abdominal surgeries. To assess the pathophysiological significance of cytokines in the mechanisms responsible for the perioperative activation of the H-P-A axis, we observed changes of plasma ACTH and cortisol levels together with those of plasma endotoxin, TNF α, IL-1 α, IL-1 β, and IL-6. In the patients who received pancreatoduodenectomy under general anesthesia, perioperative stimulation of ACTH and cortisol secretion was accompanied by asignificant elevation of plasma TNF α and IL-6 levels during and after surgical procedures. Epidural block up to the upper thoracic levels failed to suppress these stress response effectively. In the patients who received unilateral total hip replacement, the stress response of plasma hormone levels were smaller and shorter with no significant elevation of plasma cytokine levels. Similar epidural block up to the lower thoracic levels suppressed these hormonal response almost completely in this surgery. In pancreatoduodenectomy, the appearance of endotoxin in the circulating blood seemed to be responsible for the stimulated cytokine production and induced a gradual elevation of plasma TNF α and IL-6 levels. Next, we investigated the ACTH-secreting activities of these cytokines using an *in vivo* experimental system. Endotoxin and these cytokines induced marked elevation of plasma ACTH levels in conscious, freely-moving rats. These results suggest that the stimulatory effects of cytokine on the H-P-A axis is responsible for the development of the greater and more prolonged stress response of plasma ACTH and cortisol. In summary, not only neural input from the surgical wound but also the stimulation of cytokine production are responsible for the development of the stress response of H-P-A axis during and after upper abdominal surgery.

S217

Title: PLASMA CATECHOLAMINE CONCENTRATIONS BEFORE AND AFTER TRIGEMINAL RHIZOTOMY: A CLINICAL STUDY

Authors: H. Nakamura, MD, F. deBros, MD, J. Roberts, MD, M. Dershwitz, MD, W. Sweet, MD, C. Poletti MD, D. Philbin, MD.

Affiliation: HK Beecher Laboratories, Department of Anaesthesia and Neurosurgery, Harvard Medical School at the Massachusetts General Hospital, Boston, MA.

Transcutaneous selective rhizotomy by radio frequency lesion (RFL) requires analgesia during lesion induction, but an alert and cooperative patient in-between. This can result in marked hemodynamic responses, implicated as the major cause of mortality during or after RFL.

Our clinical approach has been to administer a baseline sedation (with benzodiazepines) and analgesic (narcotics) and then methohexital 0.25-0.75 mg/kg iv during stimuli. To limit blood pressure exacerbations, we have used a variety of vasodilating agents with more or less success and ease of administration. Clinically, we find that a vigorous β-blockade (as measured by the decrease in heartrate) provides optimal conditions. This study was done to follow the pattern of catecholamine secretions during the RFL procedure.

Ten patients with informed consent and institutional approval were studied. During stimulation patients received methohexital and analgesia and, either TNG, or TNG + labetalol. A third group received TNG + propranolol (1 mg/kg) over the preceding 12 hours. BP and heart rate were continuously recorded and samples obtained for plasma catecholamine concentration prior to and at the end of each RFL.

Patients receiving TNG alone (control) demonstrated significant increases in BP, HR, and catecholamine concentrations. (Figure) The addition of labetalol provided better BP control, but not consistently and wide variations continued to occur. In the beta-blocked patients (propranolol), HR, and catecholamine concentrations increased least, BP exacerbations were smaller and requirements for vasodilators were decreased.

The preoperative administration of propranolol reduces the stress induced rise in catecholamines and greatly enhancess the stability of BP and HR during RFL, rendering the general management of that particular kind of anesthesia less cumbersome.

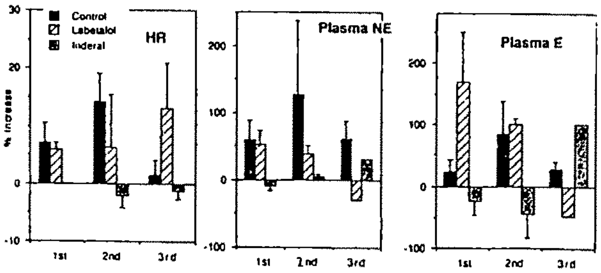

Figure 1: Percent changes for heart rate (HR) norepinephrine (NE) and epinephrine (E) during the first second and third application of RFL.

S218

Title: LASER ASSISTED TRANSDUCER ALIGNMENT

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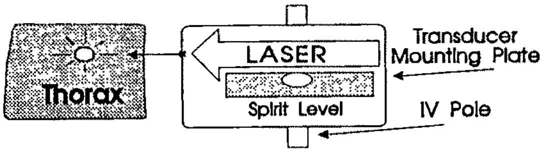
Introduction: Invasive pressure monitoring devices (A-line, PA catheter, CVP), have become routine for many pts undergoing procedures in the OR as well as for pts in ICUs. Pressure monitoring equipment is accurate when properly set up and calibrated. However, we have observed a common source of error involving the determination of the correct zero-pressure reference level. Visual adjustment of transducer [T] height to the appropriate level (mid-axilla in supine pts), is routine at our institution and may be responsible for offsets of T pressures. In an attempt to quantify this possible source of error and provide a more accurate method of adjusting T height, we developed a laser leveling device to accurately adjust Ts to the desired reference point.

Methods: HRC approval was not required; 15 measurements were obtained from 13 ICU or OR pts over a 14 day period. Each pt was evaluated for: distance of T from axilla; pressure monitored; and difference in height, [+] or [-] from zero reference point. T alignment was determined by removing the T mounting plate from its mounting and replacing it with a laser-based leveling device. This device comprised a T mounting plate to which was affixed a spirit level and a 3.0 mW 670 nm laser diode. The system was initially calibrated with a fluid-filled U-tube level at 2 meters. When the laser was leveled with the spirit level and directed at the pts axilla it illuminated a point at precisely the same level as the T.

Results: 15 A-line, 1 CVP, and 4 PA pressure transducers were evaluated in 13 pts. Mean distance from T to mid axilla was 88 +/- 11cm (SEM), Range 21-190cm. Mean absolute value of height T was in error from alignment with mid axilla was 4.9 +/- 1.2cm (SEM), Range 0.3-14.5cm.

Discussion: Our initial survey of ICU and OR patients demonstrates that errors in pressure T horizontal alignment with the phlebostatic reference point are common and may be clinically significant. Management of fluid therapy or inotropic support may be adversely affected by the relatively large errors we observed. Our laser device, assembled for less than $150.00, can eliminate this source of error.



S219

Title: NALBUPHINE AMELIORATES THE PRURITUS CAUSED BY CONTINUOUS EPIDURAL BUPIVICAINE-FENTANYL IN POST-CESAREAN SECTION PATIENTS

Authors: LM Newman PhD MD, EN Tanck MD, PB Dragisic MD, RJ McCarthy PharmD, TR Lubenow MD, AD Ivankovich MD
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Continuous epidural infusions of fentanyl/ bupivicaine [F/B] provide excellent pain relief for post-cesarean section patients. Pruritus, a common side effect of epidural narcotics, has been treated by intermittent intravenous bolus doses of nalbuphine [N]. The present study investigated whether adding N to the epidural F/B mixture would reduce the pruritus seen with F/B in post-cesarean section patients.

After institutional approval, 199 patients were assigned to one of four groups. All patients received the F/B [.001%/.1%] mixture. Fifty-two received epidural F/B only. In the three remaining groups, nalbuphine was added to the F/B to give final concentrations of: 0.0066% (N=24) [F/B/N10], 0.0132% (N=46) [F/B/N20], and 0.0264% (N=77) [F/B/N40]. All mixtures were infused between 7 and 10 cc per hour. The patients were evaluated at 24 hours post delivery for analgesia, using the visual analogue scores [VAS]. They were also monitored for the occurrence of nausea/vomiting [N/V], pruritus [PR], and sedation [SED]. Data analysis utilized ANOVA and the chi-square statistic. A value of p<.01 was considered statistically significant.

Results of postoperative evaluations for pain and the occurrences of side effects are presented in the table. There was a statistically significant reduction in the occurrence of pruritus as well as nausea and vomiting in patients receiving F/B/N40

Table 1

	F/B	F/B/N10	F/B/N20	F/B/N40
VAS	3.3	2.4	3.2	3.7
N/V	3.8%	12.5%	13.0%	0.0%[#]
PR	13.5%	12.5%	8.7%	2.6%[•]
SED	1.9%	0.0%	6.5%	2.6%

[#] p<.01 when compared to F/B/N10 and F/B/N20
[•] p<.01 when compared to F/B

These data support the notion that by mixing agonists with agonist-antagonist narcotics for epidural administration, it is possible to provide effective post-operative analgesia with minimal or no side effects.

Reference: 1. Anes Analg 67:559, 1988
2. Anesthesiology 65:216, 1986.

S220

Title: PULMONARY INJURY AFTER ISCHEMIA-REPERFUSION BY CROSSCLAMPING OF THE THORACIC AORTA IN RABBITS

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Pulmonary function has been shown to deteriorate after an ischemia-reperfusion injury to distant organs.[1,2] Leukocytes,[3] oxygen free radicals,[4] and thromboxane[5] have been implicated as possible substances inducing pulmonary injury after distant ischemia-reperfusion. To further examine pulmonary characteristics after regional ischemia-reperfusion, a clinically relevant and unique model of closed chest aortic crossclamping (CCAC) was designed.

Methods. Anesthetized rabbits with controlled ventilation were invasively monitored. CCAC was implemented by placement of a 4-French Fogarty catheter via the femoral artery into the thoracic aorta just above the diaphragm, and inflating the balloon. After 30 min of CCAC, during 2 hr of reperfusion, declamping shock was treated with sodium bicarbonate and phenylephrine to maintain acid-base and hemodynamic status near preclamp values. Lungs were harvested and bronchoalveolar lavage (BAL) was obtained for surfactant and protein analyses.

Results. Bronchoalveolar protein concentrations (mg/kg/lung) were significantly greater in the CCAC group ($n = 5$) compared to sham-operated ($n = 5$) Animals (7.23 ± 1.76 vs 2.72 ± 0.35; $\bar{x} \pm 1SEM$, $p<0.05$). Electrophoresis of BAL samples demonstrated albumin to be the predominant protein. There were no significant differences between the groups in inspiratory pressures, alveolar-arterial oxygen tension gradients, or lung wet to dry weight ratios. There was no difference in phospholipid composition of surfactant between the groups. Central venous/pulmonary arterial pressures did not increase during CCAC.

Discussion. The data suggest that the ischemia-reperfusion injury in the tissues distal to the aortic crossclamp affects the lungs. While lung function and composition of surfactant did not change, the alveolar-capillary membrane permeability increased post-clamp. This change is unlikely the result of hydrostatic forces, given that central venous/pulmonary artery pressures did not change during CCAC. Also, the absence of change in lung wet-to-dry weight ratios after CCAC does not support increased hydrostatic forces as an etiology of increased BAL proteins. In conclusion, CCAC followed by reperfusion is associated with an increase in alveolar-capillary membrane permeability without change in gross lung function.

References

1. Ann Surg 206:642, 1987
2. Surgery 106:195, 1989
3. Ann Surg 208:761, 1988
4. Surgery 105:192, 1989
5. Ann Surg 210:796, 1989

S221

Title: COMPARISON BETWEEN BEHAVIORAL AND ELECTROPHYSIOLOGICAL ASSESSMENT OF MORPHINE ANALGESIA IN RATS.

Authors: K. Nishioka, MD, Y. Harada, MD, LM Kitahata, MD, JG. Collins, PhD.
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Introduction: There are large variations in experimental methods to measure pain and evaluate the potency of analgesics. The tail-flick reflex (TFR) test is widely used in animal behavioral experiments of pain. This method is usually tested in awake animals with intact spinal conduction. In contrast most electrophysiological(EP) studies of spinal cord function are conducted in decerebrate, spinalized and/or anesthetized animals. Those differences have made it impossible to make rational comparisons between changes seen in neurophysiological experiments and behavioral tests. This investigation is designed to compare the effects of intravenous morphine on the TFR and spinal dorsal horn neuronal activity using rats with the same method of drug administration and the same noxious stimuli.

Methods: The protocol of this study was approved by the Yale Animal Care and Use Committee. The experiments were carried out on male rats (Sprague-Dawley; 300-420g). In the TFR test rats were initially anesthetized with intraperitoneal pentobarbital(PB) (40mg/kg), and a light level of anesthesia was maintained with intravenous PB(3-10 mg/kg/h). A projector lamp was focused on the blackened dorsal surface of the tail for heat stimulus, 30°C to 65°C in 8 seconds. Morphine (M) 0.2(n=10), 0.3(n=10), 0.5(n=10), 1.0(n=10) and 2.0(n=4) mg/kg was injected intravenously. Animals were examined at 5, 10, 15, 30 and 45 min after injection of each dose. Naloxone(3mg/kg) was administered at 50 minutes to examine reversal of M effects. TFR data from the dose response curves were converted to maximal percent effect (MPE) calculated using the following equation, MPE=(PR-PC)/(CT-PC)x100, where PR=postdrug response, PC=predrug control, CT=cut-off time(8 sec). A least-squares regression analysis was used to calculate the ED50 values and 95% confidence intervals of the dose response curve. In the EP test rats were anesthetized with PB in same way used in TFR test. Following tracheostomy animals were immobilized with pancuronium bromide, and mechanically ventilated. Direct arterial pressure, body temperature and $PaCO_2$ were monitored and maintained within normal limits. A laminectomy (L3-5) was performed to record extracellular single-unit activity from wide dynamic range (WDR) neurons in the dorsal horn. Noxiously evoked activity was produced by the same heat stimulus that was used in the TFR test. ED50(50%MPE) dose of M for TFR was administered intravenously(n=7). After baseline studies, the effect of M was examined at 5, 10, 15, 30 and 45 min after drug injection. Paired and student's t test was used for statistical analysis. Differences were determined to be significant with $P<0.05$. Suppression of evoked activity after drug injection was compared with control activity in terms of percent change.

Results: M suppressed the TFR significantly in a dose-dependent manner. The peak effect of intravenously administered M was observed approximately 10 minutes after administration. ED50 values with 95% confidence interval was 0.46(0.31-0.56) mg/kg. When the ED50 dose of M for TFR was administered intravenously for EP test, the peak effect was observed around 10 minutes after M administration, as seen in TFR. However, the evoked activity was suppressed by only 36.5±12.9(mean ± SE)%.

Discussion: Although many investigations have examined drug effects on animal behavior or spinal cord neurons, the differences in techniques used have made it impossible to correlate a change in one with change in the other. In this study, with the exception of surgery needed for the EP data, the conditions for the behavioral and neurophysiologic studies were similar. The results suggest that for the population of neurons studied, an ED50 dose of M for TFR study causes less than 50% suppression of neuronal activity. The results of this experiment compare the two methods and establish the standard of comparison which will aid in the evaluation and development of more effective means of spinal analgesia.

(Supported by NIH grant NS-09871)

S222

TITLE: NITROUS OXIDE ANALGESIA IN LABOUR

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AFFILIATION: Department of Anaesthesia, Toronto General Hospital, Toronto, Canada

Nitrous oxide has been used as an analgesic in labor for many years. Although several groups have reported it to be benefical (in up to 90% of patients[1]), none have used objective pain assessments. Diffusion hypoxaemia is a potential concern but has been traditionally assumed to be of minimal importance because the FiO_2 is increased when 50% N_2O:O_2 is used. However, two recent studies measuring oxygenation during N_2O analgesia in labor have recorded desaturation in 4/4 and 3/7 patients[2,3]. The aims of this study were to objectively evaluate the analgesia and effects on oxyhemoglobin saturation (SpO_2) of 50% nitrous oxide administration during labor.

Following institutional approval 10 healthy women were studied. In early labor informed consent was obtained and explanations were given regarding the visual analogue scale (VAS) pain score assessment and proper use of intermittent N_2O. When the patients requested analgesia, data was collected for 10 contractions. During the first 5 contractions the subjects breathed room air (AIR) and during contractions 6-10, N_2O was used. A VAS pain score (0=no pain; 10=worst pain) was recorded after each contraction. Pulse oximetry was used continuously. An investigator recorded the minimum SpO_2 with each contraction. O_2 desaturation (DESAT) was defined as an $SpO_2<90\%$ for ≥ 15 sec. The data are reported as mean±SEM. Students' t-test was used and $p<0.05$ was considered significant.

The subjects were 31±2 years old and were studied at 6±1 cm cervical dilation. The average VAS pain score for the group of patients while breathing AIR and N_2O are presented in TABLE 1. For individual patients the use of N_2O was associated with a significant worsening in the VAS score in 2 ($p<0.05$), significant improvement in another 2 ($p<0.05$) and no change in VAS in the remaining 6. N_2O was subjectively beneficial in 5 patients, 4 found it of no benefit and one was undecided. The mean minimum SpO_2 values for all subjects are also shown in TABLE 1. DESAT was detected in 2 patients only during N_2O use. One had 3 episodes of DESAT (mean duration 60 sec) with the lowest SpO_2=65% and the other had 1 DESAT to 89% for 15 sec.

This study suggests that objective data do not support N_2O having a beneficial analgesic effect during labor. Furthermore significant oxygen desaturation is present in some patients.

REFERENCES:
1. Br Med J 1:709-713, 1970
2. Anesth Analg 68:S167, 1989
3. Br J Anaesth 62:316-318, 1989

TABLE 1:

	SpO_2 (%)	VAS PAIN SCORE
AIR	97.2±.2	8.3±0.3
N_2O	95.5±.8	8.0±0.3
	$p<0.03$	NS

S223

TITLE: **TOTAL INTRAVENOUS ANESTHESIA WITH PROPOFOL PROFOUNDLY INHIBITS CORTISOL RESPONSE TO STRESS**

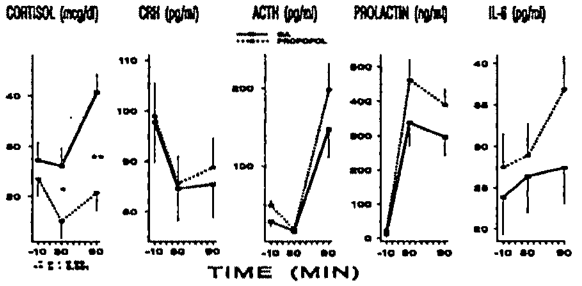
AUTHORS: D O'Flaherty, FFARCSI, A Catania, M.D., S Krishnan, AH Giesecke, M.D. and JM Lipton, PhD.

AFFILIATION: Department of Anesthesiology, University of Texas, Southwestern Medical Center at Dallas, Texas.

Surgery is a potent stimulus for the immune-endocrine axis and it is important to know the influence of specific anesthetic procedures on those host responses. The purpose of this study was to compare the effects of total intravenous anesthesia with propofol with those of conventional inhalational anesthesia on circulating cortisol, ACTH, corticotropin releasing hormone (CRH), prolactin and IL-6 production.

Forty-five healthy patients scheduled for laparoscopic tubal ligation consented to participate in this approved study. The unpremedicated patients were randomly assigned to have anesthesia induced with either propofol 2.5 mg/kg (n=24) or sodium pentothal 4 mg/kg (n=21). Anesthesia was maintained with either a continuous infusion of propofol or O_2/N_2O and isoflurane. Venous blood samples were obtained 10 min. pre-induction (-10 min, 30 min. (+30) and 90 min. (+90) post induction. Surgery did not begin until 30 minutes post induction of anesthesia so that the effects of anesthesia alone could be observed. Data were analyzed using repeated measures ANOVA.

The two groups were not significantly different with respect to age, height, weight, baseline cortisol and IL-6 plasma levels. Mean (±SEM) cortisol concentrations decreased significantly ($p<.001$) in propofol patients, but not in the inhalation group ($p=.648$) 30 min. post induction. The inhalation group had a highly significant ($p<.001$) elevation in cortisol concentrations after one hr of surgery (90 min); mean cortisol concentration, in contrast, in the propofol group returned to baseline ($p=0.27$). Circulating CRH decreased significantly at 30 ($p=.006$) and 90 min. ($p=.032$) in both groups, as did ACTH. After surgery, ACTH increased markedly and to the same extent in both groups ($P<.001$). There was a significant elevation in circulating prolactin both at 30 ($p<.001$) and at 90 min. ($p<.001$) irrespective of the anesthesia type. IL-6 levels increased significantly at 90 min ($p=.012$) with no difference between the two groups.



The results show that circulating cortisol is significantly suppressed by propofol. Because ACTH responses to surgery were similar in the two groups, the inhibition likely occurred directly on the adrenal glands. Other aspects of immune-endocrine responses to surgery were similar irrespective of anesthetic type, which further supports a specific suppression of adrenal function by propofol.

References
1. Clinical Experimental Immunology 79:470-473, 1990
2. Anesthesiology 73:308-27, 1990

S224

Title: **PREOXYGENATION: AN ALTERNATIVE TECHNIQUE**

Authors: **R Ooi, FCAnaes, J Pattison FCAnaes, P Joshi, FCAnaes, S Feldman FCAnaes, N Soni, FFARACS**

Affliation: **Magill Department of Anaesthesia, Westminster Hospital, London SW1 2AP, England**

Introduction: The standard preoxygenation techniques with a tight fitting facemask may be unacceptable for some anxious patients. This study investigates the use of a simple oxygen facemask (Hudson) with high oxygen inflow as an alternative.

Methods: With Ethics committee approval, 100 adult (ASA 1& 2) patients scheduled for elective gynecologic and orthopaedic surgery were recruited. Premedication was papaveratum (Pantopon) 10 - 20 mg and Hyoscine 0.2 - 0.4 mg 90 minutes preoperatively. These patients were randomly assigned to 2 groups: Group 1 was preoxygenated using the Magill (Mapleson A) system (100 ml/kg/min); and Group II used the Hudson mask. The Hudson mask was attached by a length of plastic corrugated tubing to the common gas outlet of an anaesthetic machine, and high flows were delivered by the oxygen flush device being held open continuously together with a setting of 8 L/min on the oxygen flowmeter. The total flows achieved were in the order of 48 L/min. The anesthetic sequence was preoxygenation (3 minutes), fentanyl 1 ug/kg, followed by thiopental 3-5 mg/kg and succinylcholine 1.5 mg/kg. Following tracheal intubation, vecuronium 0.1 mg/kg was given. Ventilation was not assisted and the tracheal tube was left open to room air until the patients' oxyen saturation reached the study end point of 93%. During the period of apnoea, anesthesia was maintained by incremental doses of thiopental 25 - 50 mg, at 2 minute intervals. Oxygen saturation was measured using finger pulse oximetry (Ohmeda 3700E). The measurements taken include oxygen saturation prior to and immediately following preoxygenation, and the time taken to fall to 95% and 93% saturation. Results were analysed using ANOVA and the Mann-Whitney U test (level of significane : $p< 0.05$)

Results: The two groups were comparable in terms of age, weight, height, smoking habits, oxygen saturation, before and after preoxygenation. The times to 95% and 93% saturation were not significantly different between the two groups.

Discussion: Our results indicate that the Hudson mask system with high oxygen inflow offers an alternative to the current techniques of preoxygenation.

Table 1: Mean (SD) oxygen saturation (before and after 3 minutes preoxygenation) and time to reach 95% and 93% saturation.

	SaO_2 Air	SaO_2 oxygen	95% SaO_2 time (sec)	93% SaO_2 time (sec)
Group 1	96.3 (2.0)	99.8 (0.6)	226.4 (83.2)	248.7 (90.3)
Group II	96.8 (2.4)	99.8 (0.6)	232.6 (80.9)	254.3 (87.3)

Acknowledgements: SIMS medical research fellowship (England)

S225

Title: **WHAT DO PATIENTS WANT? — PREFERENCES FOR IMMEDIATE POSTOPERATIVE RECOVERY**

Author: **Fredrick K. Orkin, M.D.**

Affiliation: **Department of Anesthesia, University of California (San Francisco) School of Medicine**

Introduction: Much is known about the common symptoms accompaning uncomplicated surgical anesthesia. Pharmacologic adjuvants and alternative techniques can reduce the incidence of undesired side effects but may also have associated morbidity as well as increased cost. Yet, what concerns *patients*? What do patients *want*? In an imperfect world in which some morbidity may be unavoidable, this study sought to determine the preferences of would-be patients for immediate postoperative recovery, to assist in planning anesthesia care more satisfying to patients.

Methods: The decision making of individuals was studied using conjoint analysis, a multivariate statistical technique which determines the relative importance (utility) of decision attributes (factors) at different severities (levels) and the way they are used during actual decisions. Subjects ranked ("best to worse") highly structured scenarios drawn from a matrix of factors at several levels:

Factors	Levels			
1 Mental acuity	awake	drowsy	asleep	
2 Pain	none	mild	moderate	
3 Emetic symptoms	none	nausea	vomiting	
4 Muscle aches?	no	yes		
5 Dysphoria?	no	yes		
6 *Extra* cost to pt.	none	$15	$35	$50

Given an unmanageable number of possible scenarios, a fractional factorial design enabled analysis of first-order effects with only 16 scenarios; 4 additional scenarios, not used for analysis, were included to validate the computed utilities. Other multivariate techniques (e.g., cluster analysis) were used to study the different decision-making patterns noted. To date, 47 subjects have participated: nurses, anesthesiologists, and support staff at two teaching hospitals, and computer personnel at a national meeting.

Results: Subjects completed the ranking in 15 minutes of intense concentration. From the utilities, each factor's importance (as a % in the preference decision) was calculated; for the overall group: *1*, 5%; *2*, 18%; *3*, 40%; *4*, 11%; *5*, 16%; *6*, 10%. Compared to actual rankings, predicted preferences of the 4 holdout scenarios agreed well (for group: r=0.998, *P*=0.0010). Preferences did not differ by gender, job category, age, history of prior surgery, or study site. However, preference patterns differed by the principal factor used by each subject (expressed as a % of subjects using a given factor): *1*, 4.3%; *2*, 8.5%; *3*, 72%; *5*, 4.3%; *6*, 2.2%; two factors, 8.5%. Subjects were generally quite willing to accept a variety of "trade-offs" — dysphoria, increased cost, decreased mental acuity, and/or increased pain — to avoid nausea and vomiting.

Discussion: Given the improved safety of anesthesia care, serious complications are very infrequent, if not rare, and, thus, quality of care is equated increasingly by patients with the absence of minor, but disturbing side effects, such as those studied here. Although a larger and perhaps more varied group of subjects might enable an explanation of observed preferences for postoperative recovery, the preferences expressed have important implications for planning anesthesia care more satisfying to patients. That almost three-quarters of subjects based their preferences primarily on whether emetic symptoms were present suggests that greater efforts should be made to prevent these symptoms. Such efforts might include preferentially using drugs associated less with such symptoms, avoiding offending drugs, and/or using prophylactic agents, even if such behavior leads to dysphoria, increased cost, decreased mental acuity, and/or increased pain. A prospective study, including *patient* assessment of care, is needed to validate this approach to improving anesthesia care.

S226

TITLE: EFFECTS OF NICARDIPINE ON MAXIMAL VENTRICULAR ELASTANCE (Emax) AND MAXIMAL ARTERIAL ELASTANCE (Ea) IN HUMANS

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To distinguish between direct myocardial actions of nicardipine and peripheral actions, we studied the effects of nicardipine on Emax, which is a measure of contractility independent of loading conditions, and on Ea, which is a measure of arterial load independent of ventricular function (1).

METHODS: After institutional review board approval and informed concent, 30 μg/kg of nicardipine was administered intravenously (IV) in 14 surgical patients with intraoperative hypertension (systolic BP>150 mmHg or diastolic BP>90 mmHg). Before (baseline) and 3 min after nicardipine IV, hemodynamic variables including mean arterial BP (MABP), systemic vascular resistance (SVR), stroke volume index (SVI), ejection fraction (EF), and cardiac index (CI) were measured (or calculated) using balloon tipped pulmonary artery catheter and transesophageal echocardiography. Based on the study of Sunagawa et al (1,2), we then calculated Emax and Ea using the hemodynamic data obtained before (baseline) and 3 min after nicardipine IV.

RESULTS: Nicardipine produced significant decreases in MABP and SVR, and significant increases in SVI, EF, and CI (Table 1). Other hemodynamic variables did not change significantly. Three min after nicardipine IV, the slope of Ea decreased, whereas the slope of Emax did not change significantly (Table 2).

Table 1 (mean±SD, n=14):

	Baseline	3 min
MABP (mmHg)	111±20	85±16 *
SVR (dynes·sec/cm^5)	1574±368	847±215 *
SVI (ml/beat/m^2)	37±7	47±8 *
EF (%)	53±12	73±10 *
CI (L/min/m^2)	3.6±0.7	4.8±1.1 *

* different from baseline (P<0.05)

Table 2 (mean±SD, n=14):

	Baseline	3 min
Emax (mmHg/ml)	2.86±1.35	3.73±2.01
Ea (mmHg/ml)	-2.52±1.00	-1.21±0.45 *

* different from baseline (P<0.05)

DISCUSSION: These data suggest that nicardipine is a relatively selective vasodilator with minimal direct myocardial actions in humans.

REFERENCES: 1) Anesthesiology 74: 172, 1991;
2) Am J Physiol 245: H 773, 1983

S227

Title: THE EFFICACY OF PREOPERATIVE PREPARATION AND THERAPEUTIC SUGGESTION ON POSTOPERATIVE OUTCOME AFTER BRIEF AMBULATORY SURGERY

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Affiliation: Department of Anesthesia, The University of Iowa, Iowa City, IA

Introduction: The objective of this prospective, randomized and double blind study was to examine the hypothesis that preoperative preparation (PP) combined with intraoperative therapeutic suggestion (TS) could be utilized in ambulatory surgical patients to improve their outcome in the recovery period and to expedite "home-readiness".

Patients under general anesthesia can register sounds and these may be beneficial to the recovery.[1,2] In inpatients research on the effects of TS on outcome has yielded conflicting conclusions.[1,3,4] Some studies have confirmed, and others have not, that discharge from the hospital can be augmented with the aid of TS during anesthesia. Generally, in these studies neither the anesthesia methods nor the postoperative care were standardized.

Since the work of Egbert et al, many anesthesiologists believe that PP before surgery outlining the general plan for the anesthesia and surgery, and advise of the benefits of postoperative relaxation can reduce preoperative anxiety, pain and hospital stay.[5]

The beneficial implications of improved outcome with PP and TS would be enormous. In addition to improving patients' outcome and comfort, escalating hospital costs could be contained with these nonpharmacologic means.

Methods: With University Investigation Committee approval, written informed consent was obtained from 41 unpremedicated ASA class I patients scheduled for laparoscopic tubal ligation, and randomized to the PP/TS group or the control group.

Both groups received a standard preoperative informed consent. The PP/TS group, in addition, received extensive information about the perioperative events. This included discussion about the pain, nausea, and vomiting the patient may experience and how to alleviate it. The patients were ensured that adequate therapy was readily available. Equal amount of preoperative time was spent with both groups.

During surgery both groups listened to a audio tape. The PP/TS tape contained an authoritative/suggestive talk about faster and safer recovery. The benefits of early urination and ambulation with respect to early discharge were emphasized. The control tape contained operation room noise without any discussion. The anesthetic drugs used were thiopental, alfentanil, N_20 and vecuronium bromide. Alfentanil infusion rate was adjusted to maintain hemodynamic variables within 20% of awake measurements.

After extubation, times to response to command, orientation, ability to sit, drink, walk, urinate, and "home-readiness" were recorded. The Aldrete score was recorded. Nausea, retching, vomiting and pain was evaluated every 15 min. Pain medications and antiemetics used were recorded. The patients' anxiety (Spielberger Anxiety Profile), mood (Profile of Mood States), and the metabolic stress reaction (cathecholamines, cortisol) were evaluated prior to surgery and at discharge. The data was analyzed with ANOVA and chi^2 test.

Results: The main results (mean±SD) can be seen in the table. No statistically significant differences were noted between the groups in any of the outcome variables. The hemodynamic profile during the operation and in the PACU were similar between the groups.

	PP/TS group	Control group
N	23	18
Age	29±5.6	29±4.7
Weight (kg)	64.7±8.1	68.8±16.2
Duration of Anesthesia (min)	49±16	46±8
"Home-ready"(min)	190±69	189±55
Ability to drink(min)	70±46	83±43
Ability to walk(min)	139±42	134±36
Ability to urinate(min)	165±59	163±57
N/V in PACU (%) of patients	81.8%	77.8%

Discussion: Recovery and "home-readiness" after ambulatory surgery are influenced by many factors such as age, sex, the nature and duration of the operation, the type of anesthesia and the use of opioid analgesics. These variables were standardized as much as possible under the clinical conditions of the present study.

We hypothesized that recovery from surgery and anesthesia may be aided by offering the patient more behavioral and cognitive control over the entire event with extensive imformation about the procedure (PP) and unconsciously with the aid of TS.[1,2,3,4] This hypothesis was not supported by our results which showed no significant differences in the the patients' subjective or objective recovery in any of the variables measured.

References: 1. Lancet 1988;2:491. 2. Br J Anaesth 1989;62:645. 3. Br. J Anaesth 1988;60:697. 4. Acta Anaesthesiol Scand 1987;31:567. 5.N Eng J Med 1964:270:825.

S228

Title: INTRATHECAL FENTANYL SUPPLEMENTATION OF EPIDURAL ANESTHESIA FOR CESAREAN SECTION

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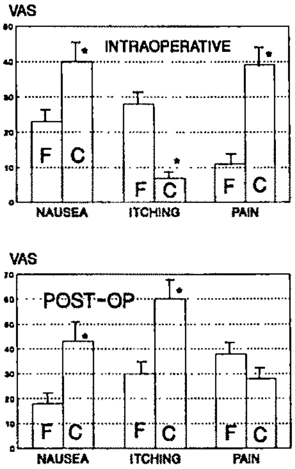
Affiliation: Dept of Anesthesiology, New York University Medical Center, NY, NY 10016

Introduction: This study assesses if intrathecal fentanyl supplementation improves the quality of lumbar epidural anesthesia (LEA) for cesarean section (CS).

Methods: Following approval by the Review Board, informed consent was obtained from 36 women undergoing elective CS under LEA. In Group I (n=21), a #17g Hustead needle was introduced into the lumbar epidural space. A Sprotte needle (#24g, 120 mm) was inserted through the epidural needle to puncture the dura and inject fentanyl 30 μg intrathecally. The spinal needle was withdrawn and an epidural catheter inserted. Two hours later, 5 mg epidural morphine (EM) was given. In Group II (n=15), patients received only LEA + EM. A blinded observer used a visual analog scale (VAS) to assess Nausea (N), itching (I) and surgical pain (SP) intraoperatively and 24 hours later. Intraoperative shivering was evaluated on 0, +, ++, +++ scale. The results (mean±1 SE) were analyzed using Mann-Whitney rank-sum test.

Results: Intraoperatively, scores for N, SP and shivering were lower, and scores for I greater in Group I compared to Group 2 (Fig). However, on postop day #1, Group I had lower scores for N and I than did Group II ($p<0.05$) with no significant difference in SP (Fig). No patient developed headache.



Legend: F=fentanyl; C=controls. *=$p<0.05$

Discussion: Intrathecal fentanyl supplementation improves the quality of LEA and decreases shivering as well as the side effects of EM. The decrease in the EM side effects may be due to acute tolerance induced by prior exposure of μ receptors to fentanyl.

S229

Title: FIBEROPTIC VS. RIGID LARYNGOSCOPY FOR RAPID SEQUENCE INTUBATION OF THE TRACHEA

Authors: A Ovassapian, MD, TC Krejcie, MD, CW Joshi, MD

Affiliation: Anesthesia Department Northwestern University, and VA Lakeside Medical Center, Chicago, IL

INTRODUCTION: The question has been raised whether unexpected failure of rigid laryngoscopy during rapid sequence induction can be resolved using a fiberscope. To answer this question a study was carried out comparing intubation time and success rate using rigid and fiberoptic laryngoscopy.

METHODS: After institutional approval, 24 PS 1 or 2 patients were randomly assigned to either the fiberoptic or rigid laryngoscopy group. Patients were not at increased risk of aspiration, but were treated as such for the purpose of the study. Routine monitors were applied. After preoxygenation anesthesia was induced with thiopental 5 mg/kg and succinylcholine 1.5 mg/kg to facilitate tracheal intubation. One assistant applied cricoid pressure, while a second assistant helped with the intubation. A chart recorder was used to record the ECG tracing and time the sequences of intubation. Ease of laryngeal exposure, attempts and outcome of each intubation were recorded. If the assigned intubation technique failed on three attempts the alternate technique was applied.

RESULTS: Intubation Data	Fiberoptic	Rigid
	Mean ± SD	
1st attempt intubation	11	11
Intubation time (sec)	19±8	13±4*
Apnea time (sec)	44±15	32±7*
3rd attempt intubation	1	0
Failed intubation	0	1**

*Significant at $P < 0.05$

** Intubated on the first attempt using the fiberscope

DISCUSSION: Fiberoptic laryngoscopy was demonstrated to be an acceptable means of rapid sequence induction and intubation in patients simulated to be at risk of aspiration. Intubation and apnea times with fiberscope were significantly longer ($P < 0.05$) than rigid laryngoscopy, however, from clinical perspective the two approaches were not different and no patient showed oxygen saturation of less than 96%. These findings support the usefulness of the fiberscope as an alternative method for airway management when the anesthesiologist encounters an unexpected failed rigid intubation. In patients with full stomach in whom general anesthesia is the choice but awake intubation is not desirable or possible, fiberoptic intubation may be extremely useful.

S230

TITLE: KETAMINE BUT NOT PROPOFOL IMPAIRS LEFT VENTRICULAR DIASTOLIC FUNCTION IN CHRONICALLY INSTRUMENTED DOGS

AUTHORS: PS Pagel MD, WT Schmeling MD PhD, JP Kampine MD PhD, DC Warltier MD PhD

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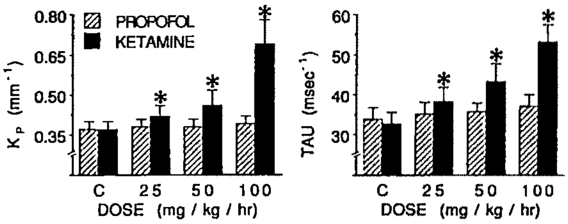
The effects of intravenous anesthetics on left ventricular diastolic function *in vivo* have not been described. Diastolic mechanics significantly influence overall cardiac performance and diastolic dysfunction may precede or contribute to abnormalities in systolic function in various pathological states. This investigation explored the direct effects of ketamine (K) and propofol (P) on active (isovolumetric relaxation) and passive (regional chamber stiffness) indices of diastolic function in dogs with pharmacologic blockade of the autonomic nervous system (ANS).

With prior Animal Care Committee approval, anesthetized dogs (n=7) were instrumented for measurement of aortic and left ventricular pressure, dP/dt, cardiac output and subendocardial segment length. Dogs were allowed to recover from surgery for 7 days prior to experimentation. The ANS was blocked with propranolol (2 mg/kg), atropine methylnitrate (3 mg/kg) and hexamethonium (20 mg/kg). Ventricular relaxation was characterized by the time constant of isovolumetric relaxation (Tau). Regional chamber stiffness (K_p) was described using an exponential equation relating ventricular pressure to segment length between minimum ventricular pressure and onset of atrial systole. Dogs were anesthetized with K or P (10 mg/kg, i.v.) in a random fashion. Anesthesia was maintained with a continuous infusion of K or P at 25, 50 or 100 mg/kg/hr in a random order. Measurements were recorded in the conscious state and 20 minutes after equilibration at each anesthetic dose. Changes between the conscious control (C) and anesthetic interventions were compared by ANOVA with repeated measures followed by Bonferroni's t-test (*p<0.05).

In the presence of ANS blockade, P produced decreases in heart rate, mean arterial and left ventricular systolic pressure, and rate pressure product. K also resulted in decreases in heart rate and rate pressure product but also increased systemic vascular resistance and left ventricular end diastolic pressure at higher doses. K caused a dose-dependent increase in Tau and K_p whereas P had no effect. (figure).



The results indicate that K but not P produces left ventricular diastolic dysfunction. K prolonged isovolumetric relaxation and increased regional chamber stiffness, suggesting that ventricular filling may be altered by at least two mechanisms in the presence of K. In contrast, P produced no change in either index of diastolic function in the chronically instrumented dog with ANS blockade.

S231

TITLE: KETAMINE DEPRESSES MYOCARDIAL CONTRACTILITY AS EVALUATED BY PRELOAD RECRUITABLE STROKE WORK IN CHRONICALLY INSTRUMENTED DOGS

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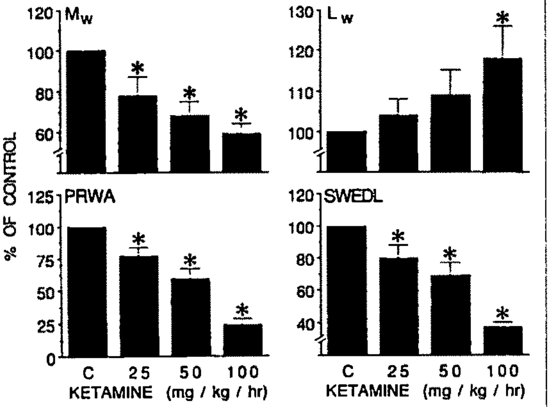
Investigations examining the direct effects of ketamine (K) on myocardial contractility *in vivo* suggest that K may produce depression of contractile function but are limited because K produces sympathomimetic effects. Previous studies also used indices of contractility which were either indirect indicators of inotropic state or were significantly load dependent. This investigation explored the direct actions of K on myocardial contractility in dogs with pharmacologic blockade of the autonomic system (ANS).

With prior Animal Care Committee approval, anesthetized dogs (N=6) were instrumented for measurement of aortic blood pressure, left ventricular pressure, +dP/dt, cardiac output, and regional contractility (ultrasonic segment length transducers). Dogs recovered for 7 days prior to experimentation. The ANS was blocked with propranolol (2 mg/kg), atropine methylnitrate (3 mg/kg), and hexamethonium (20 mg/kg). Abrupt occlusion of the inferior vena cava *via* a hydraulic occluder was performed in order to generate ventricular pressure-segment loops in the conscious and anesthetized states. Contractility was assessed using the preload recruitable stroke work (PRSW) versus end diastolic length (EDL) relationship, and two derived variables, preload recruitable work area (PRWA) and stroke work at constant end diastolic length (SWEDL). Dogs were anesthetized with K (10 mg/kg, iv) and maintained with a continuous infusion of K at 25, 50, and 100 mg/kg/hr in a random fashion. Measurements were repeated after 20 minutes of equilibration at each anesthetic dose. Changes between the conscious control (C) and anesthetic interventions were compared with ANOVA with repeated measures followed by Bonferroni's t-test (*p<0.05).

In the presence of ANS blockade, K produced significant decreases in heart rate and rate pressure product and increases in left ventricular end diastolic pressure and systemic vascular resistance. K caused a dose-dependent decrease in myocardial contractility as evaluated by PRSW vs. EDL slope (M_W), PRWA, and SWEDL. Length intercept (L_W) increased at the 100 mg/kg/hr dose (figure).



The results indicate that K produces direct depression of myocardial contractility in chronically instrumented dogs independent of changes in autonomic nervous system activity. The negative inotropic actions of K can be quantitated using the PRSW relationship and derived variables.

S232

TITLE: SPINAL FLUID RETURN RATE IN SPINAL NEEDLES

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In our hospital, we have found that the slow spinal fluid return rate from the spinal needles may have partly resulted in unnecessary repeated dura punctures. This study evaluated the rate of spinal fluid return in different spinal needles with different needle orientations.

The 3.5-inches spinal needles under testing were: Quincke 25G and 27G (QU25G, QU27G), Whitacre 25G(WH25G), and Sprotte 24G(SPR24G). A colored-water column of 200mm high was built within a solid PVC tubing to emulate the spinal fluid pressure. A one cm diameter hole was created on the side of the PVC tubing and covered with a thin membrane. Each spinal needle was placed in an adjustable holder and introduced perpendicularly into the 200 mm water-column by puncturing through the membrane-covered hole. Each spinal needle was introduced through the membrane in three different orientations -the bevel or the distal orifice of the needle facing upward, downward and laterally respectively. Rate of fluid returning from the spinal needles was measured by: 1. the time when the fluid was first seen in the hub of the needle; 2. the time for each of the first six drops of fluid collected; and 3. the time for 1 c.c. of fluid collected. Five needles of each type were tested. Each needle with each orientation was repeated five times. Data were analyzed with unpaired t-test, ANOVA and Tukey test as appropriate.

The time for first drop of fluid collected and the time for 1 c.c. of fluid collected were shortest for Sprotte 24G, followed by Whitacre 25G, Quincke 25G and Quincke 27G respectively (fig 1 & 2) with statistically significant differences (p<0.05). Whitacre 25 G has significantly (p<0.05) shorter spinal fluid return time than Quincke 25G. The time for return fluid first seen in the hub of the needles was significantly shorter (P<0.05) for Sprotte 24G and Whitacre 25G needles than the Quincke needles. The orientation of the bevel or the orientation of the distal orifice did not affect the spinal fluid return time. This data suggested that the Sprotte 24G needle is the choice of spinal needle to obtain the quickest spinal fluid return among the needles tested. Future spinal needle design can improve the hub of the needle for better visibility of fluid return; and can improve the distal orifice to allow better spinal fluid return and may decrease some of the unnecessary repeated dura punctures.

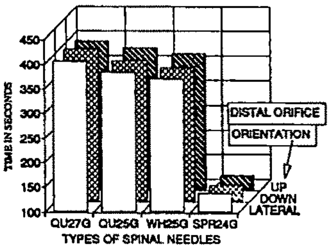

Fig 1. Average Time for 1c.c. of Spinal Fluid Return

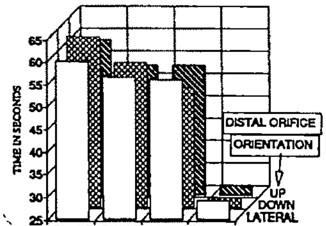

Fig 2. Average Time for First Drop of Spinal Fluid Return

S233

Title: THE ROLE OF PAIN AS A CAUSE OF POSTOPERATIVE NAUSEA/VOMITING AFTER OUTPATIENT ANESTHESIA

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Postoperative nausea and vomiting (PNV) are frequent side effects of outpatient general anesthesia (GA). The etiology of PNV is multifactorial, including anesthetic agents, type of surgery, and patient predisposition. Pain has been cited as a cause of PNV based on an inpatient study of abdominal surgery(1). The purpose of this investigation was to evaluate the role of pain on PNV in ambulatory knee arthroscopy.

With HIC approval, 233 outpatients receiving GA for knee arthroscopy were prospectively evaluated. Anesthetic induction was with thiopental and succinylcholine, and maintained with isoflurane/N_2O/O_2, and 1-2 μg/kg fentanyl. Data on the occurrence of pain and PNV was collected in the 1st stage recovery(PACU), and the 2nd stage outpatient recovery room(OPRR), by personnel uninvolved in the study. Pain treatment(Rx) and anti-emetics were also documented. Data was analyzed by χ^2 and significance set at $P<0.05$.

The incidence of pain reported in PACU and OPRR was similar (31.7% vs 35.7%). There was no difference in the incidence of PNV between patients with pain and those without. This held true even when subdivided into patients with pain of severity to require Rx (Table 1). In the PACU patients treated for pain, 47.5% were pain free in the OPRR. The incidence of PNV in those patients who continued to report pain in the OPRR despite analgesia treatment in the PACU was similar to those who were pain free (29% vs 25%).

In contrast to the previous study(1), we were not able to show that pain is a major contributor to PNV, though we have reconfirmed that narcotic Rx of pain does not increase PNV. The differences in these studies likely reflect the different sites and magnitude of the surgery. Patients with pain from abdominal surgery may be more prone to PNV than from peripheral site surgery. Severity of pain is a possible confounding factor, but we also evaluated patients with pain of severity to require Rx and found no differences.

Table 1: Incidences of PNV

	N*	PACU	N*	OPRR
Pain	69	11.6%	79	25.3%
No Pain	149	14.1%	142	21.8%
Severe Pain	59	11.9%	59	16.9%

*N= total pts in each of the 3 categories

Ref: Can Anesth Soc J 23:366, 1976.

S234

TITLE: A DOSE DEPENDENT REDUCTION IN HALOTHANE M.A.C. IN RATS WITH A COMPETITIVE N-METHYL-D-ASPARTATE (NMDA) RECEPTOR ANTAGONIST

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Introduction: The primary site of action of the dissociative anesthetic agents, ketamine and phencyclidine remains unclear. Recently, it has been shown that these agents bind non-competitively to the NMDA class of receptors[1]. It is unclear, however, that specific antagonism of the NMDA receptor results in any anesthetic actions. In the present study, the effect of a competitive NMDA receptor antagonist, 4-(3-phosphonopropyl)-2-piperazinecarboxylic acid (CPP) on halothane M.A.C. was examined in rats. Neurobehavioral and tail flick latency (TFL) effects of CPP were also studied.

Methods: Subjects were adult male Sprague-Dawley rats. CPP was administered i.p. to awake rats at doses of 10, 30, 60, 90 and 120 mg/kg. Neurobehavioral effects and TFL were observed in these subjects. The same doses of CPP (n=6 at each dose) were then administered to rats anesthetized with halothane and mechanically ventilated. A group of 10 rats injected with placebo served as controls. The femoral artery and vein were cannulated to monitor and control arterial blood gases and blood pressure. Halothane M.A.C. (tail clamp method) was determined as previously described[2]. Intergroup comparisons of halothane M.A.C. values were made using ANOVA and the Student-Newman-Keuls test. TFL values were compared using the Kruskal-Wallis test. A p-value < 0.05 was considered significant.

Results: Nystagmiform head and eye movements were observed at all doses of CPP. Loss of righting reflex occurred at doses greater than 10 mg/kg. Absence of spontaneous movements was observed at the highest dose. Neurobehavioral effects persisted for 3/4-1 h. TFL did not differ significantly from control values at any dose of CPP. Halothane M.A.C. (0.95± 0.02 vol % in controls) decreased significantly ($p < 0.01$ in all treatment groups) and in a dose dependent manner with CPP treatment, reaching a minimum value of 0.21 ± 0.05 vol% at 90 mg/kg. There were no significant differences in arterial pH, PaO_2, $PaCO_2$, blood pressure or heart rate between treatment groups.

Conclusions: CPP, a selective and competitive NMDA receptor antagonist markedly decreases halothane M.A.C. in the rat. This provides further support for the NMDA receptor as yet another class of receptors in the central nervous system that may mediate anesthetic actions. This also represents a new class of possible anesthetic agents, competitive, as opposed to noncompetitive NMDA receptor antagonists. The TFL results suggest that CPP is not, however, a typical analgetic agent.

References:
1. Proc Natl Acad Sci USA 83:7104-7108, 1986
2. Anesthesiology 53:315-334, 1980

S235

TITLE: Transtracheal Doppler: A Safe Technique?

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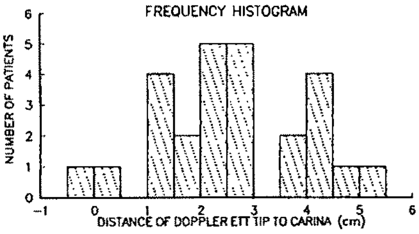
Transtracheal Doppler (TTD) has recently been introduced as a noninvasive and continuous method to monitor cardiac performance. TTD utilizes an endotracheal tube (ETT) with a 5mm Doppler transducer mounted on its tip. The transducer must be pressed flush against the tracheal wall and the depth of the Doppler ETT adjusted to obtain optimal Doppler signals. While several investigations are examining the validity of this technique, its safety has yet to be established. The manipulations required to position the Doppler ETT risk extubation and the ETT location where optimal Doppler signals are obtained may jeopardize ventilation (eg., endobronchial intubation). Also, the Doppler transducer may result in tracheal injury and post-operative airway complications. Therefore, we undertook the following study to prospectively evaluate the safety of TTD.

Methods: Following ethical committee approval, TTD monitoring was performed in 26 surgical patients using an ABCOM-1 (Applied Biometrics) device. Following induction of general anesthesia, the Doppler ETT was placed in the trachea and adjusted to obtain optimal Doppler signals. ETT depth, measured at the incisors, was recorded. Fiberoptic examination was performed to determine the distance from the ETT tip to the carina and to detect evidence of tracheal injury. On the first post-operative day, patients were examined for airway complications. Post-operative examinations were also performed in a control group of 27 patients who underwent general anesthesia with a standard ETT (Sheridan). ETT cuff pressure was monitored in both groups. Analysis includes descriptive statistics and Student's t-test.

Results: Adequate Doppler signals were obtained in all 26 patients. The mean Doppler ETT depth was 22.5 ± 1.1 cm in women and 23.4 ± 1.9 cm in men. The mean distance from Doppler ETT tip to carina was 2.7 ± 1.3 cm (see histogram). TTD monitoring resulted in one endobronchial intubation (3.8%), no extubations, tracheal hyperemia in 4 patients (15%) and no tracheal ulcers. Analysis of post-operative data show a 32% (8/25) incidence of sore throat and/or hoarseness in the Doppler group compared to 48% (13/27) in the control group (p=NS).

Discussion: Our results indicate that Doppler signals are reliably obtained with the transtracheal approach. The Doppler ETT is often positioned at a greater depth, and nearer to the carina, than recommended.[1] Vigilance for detection of endobronchial intubation, therefore, is advised during TTD monitoring. The Doppler ETT does not increase the incidence of post-operative airway complications.

Reference: 1.Anesthesiology 67:255-257,1987



S236

TITLE: Transtracheal Doppler: Validity of Intraoperative Measurements

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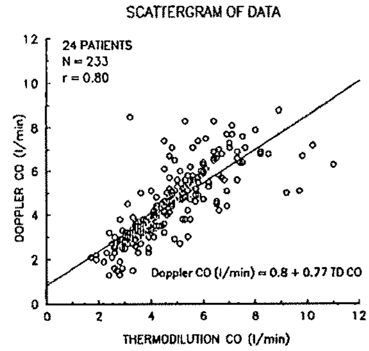
Introduction: Transtracheal Doppler (TTD) is a new method for continuous monitoring of cardiac output (CO). TTD utilizes a 5 MHz pulse-wave Doppler transducer mounted on the tip of an endotracheal tube (ETT) to measure the diameter of and blood flow velocity within the ascending aorta. A prospective evaluation to determine the accuracy, trending capability, and operator learning curve for TTD by comparison to thermodilution (TD) is described.

Methods: Following an ethical committee approved protocol, TTD monitoring (ABCOM-1, Applied Biometrics) was performed in 27 patients undergoing non-cardiac surgery. After induction of general anesthesia, the Doppler ETT was inserted and the position adjusted to obtain optimal Doppler signals. Once positioned, TTD provides continuous display of CO as well as an audible broadcast of the received Doppler signal.

As a reference standard, TD measurements were obtained at end-expiration using room temperature injectate and a SpaceLabs TD CO computer. The TTD operator was blinded to the TD measurements. Simultaneous TD and TTD CO measurements were compared using regression analysis, the method of Bland and Altman, and F-test for comparison of variances. A p-value of less than 0.05 was considered significant.

Results: Adequate Doppler signals were obtained in 24 of the 27 patients. Analysis of Doppler and TD CO data reveals a correlation coefficient r=0.80, a mean bias of -0.28 l·min^{-1}, and a standard deviation of the bias (SD) of 1.03 l·min^{-1} (see fig.). Trending data shows a strong correlation between changes in TD CO and changes in Doppler CO (r=0.74). In the subgroup of patients whose Doppler signal quality was rated excellent (11 pts), the agreement between Doppler and TD was significantly improved (r=0.92, SD=0.61 l·min^{-1}). Operator experience also effected TTD performance. TTD had significantly less error in the second half of the study (SD=1.0 l·min^{-1}) compared to the first half (SD=1.4 l·min^{-1}).

Discussion: Adequate TTD signals were unobtainable or of suboptimal quality in a significant percentage of patients undergoing non-cardiac surgery. In those patients where the Doppler signal quality was excellent, TTD CO values were in close agreement with matched TD values. Increased operator experience also improved TTD performance. Modifications in TTD technology, including refined transducer design and signal processing, are currently being explored to improve the reliability of this device.



S237

Title: MOLECULAR CLONING AND EXPRESSION OF A RAT A2 ADENOSINE RECEPTOR

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Adenosine is a putative neurotransmitter whose actions appear to be mediated by G protein-linked receptors. Two subtypes of adenosine receptors are distinguished by ligand binding profiles and by opposing effects on cAMP accumulation. Activation of the A2 receptor is associated with an increase in intracellular cAMP. A full understanding of adenosine receptor signal transduction mechanisms requires structural characterization of the receptor molecule and its gene. With PCR cloning we have isolated a rat cDNA encoding a functional member of the class of G protein-linked receptors with characteristics of an A2 receptor.

Methods: Degenerate oligonucleotide primers corresponding to conserved transmembrane domains of G protein-linked receptors were used in PCR reactions to amplify fragments of related genes from rat brain first strand cDNA. One fragment which selectively detected striatal mRNA in Northern blot analysis was used to screen a rat striatal cDNA library. A full length cDNA was isolated, sequenced and expressed.

Results: The rat receptor cDNA predicts a 410 amino acid protein with seven putative hydrophobic regions consistent with the transmembrane domain organization of a G protein-linked receptor. Alignment with the putative canine A2 receptor (1,2) reveals 84% identity at the nucleic acid level, 96% amino acid identity in the putative transmembrane domains and 82% overall amino acid identity. Lesser degrees of homology are seen in comparisons with the adenosine 1, β2 adrenergic and D2 dopaminergic receptors. Sequence deviation between the rat and canine A2 receptor is greatest at the carboxy terminus of the predicted protein. Potential phosphorylation sites are predicted within the carboxy terminus. *In situ* hybridization analysis demonstrates selective expression in rat striatum, accumbens and olfactory tubercle consistent with the ligand binding and receptor autoradiograph profiles for the A2 receptor. Transfected COS cells express a ligand binding moiety with a pharmacologic profile consistent with an A2 receptor.

Discussion: The A2 receptor subtype may mediate some of the physiologic actions of adenosine in the brain and in the periphery. Isolation and characterization of a rat A2 receptor cDNA supports a G protein-linked signal transduction mechanism and provides a reagent for studies on receptor mechanisms, pharmacology, anatomic distribution and gene expression.

References: 1)Science, 1989; 244:569
2)BBRC, 1990; 173:1169

S238

TITLE: DOES DROPERIDOL OR MIDAZOLAM REDUCE THE INCIDENCE OF ALFENTANIL-ASSOCIATED POSTOPERATIVE EMESIS?

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Introduction: A continuous infusion of alfentanil has desirable pharmacokinetic properties that make it a useful anesthetic in children. However, children anesthetized with alfentanil have a higher incidence of postoperative nausea and vomiting than those anesthetized with halothane. Droperidol (D) has been demonstrated to reduce the incidence of postoperative emesis in children undergoing strabismus surgery. Preliminary studies suggest that midazolam (M) also may reduce the incidence of postoperative emesis. This randomized blinded study was designed to evaluate the effectiveness of D and M compared with placebo (P) in reducing the incidence of postoperative emesis in children receiving continuous alfentanil infusions for dental procedures.

Methods: After our institution's IRB approval and written, informed consent from a parent, 44 ASA I-II patients aged 2-12 years scheduled for elective complete oral rehabilitation were randomized into one of 3 groups. All groups underwent inhalation induction with halothane/N_2O 70%/O_2 30%. After the induction of anesthesia, atracurium 0.5 mg/kg and atropine 10 µg/kg were administered intravenously. Halothane was then discontinued, and an intravenous bolus of alfentanil (100 µg/kg) was administered followed by an infusion at 2 µg/kg/min. Supplemental alfentanil boluses of 10 µg/kg were given in response to hemodynamic changes greater than 20% above baseline. After induction and before surgical incision patients in group D received 75 µg/kg of droperidol; patients in group M received 0.25 mg/kg of midazolam with a maximum dose of 4.0 mg; patients in group P received an equal volume of normal saline.

The following parameters were recorded: heart rate and blood pressure during induction and incision; duration of anesthesia and surgery; times to wakefulness and extubation; oxygen saturation and respiratory rate during recovery room stay; duration of recovery room and outpatient unit stay; and postoperative analgesia requirements. The frequency of nausea and vomiting in the recovery room and outpatient unit was also recorded. All data were analyzed with analysis of variance and chi-square. Significance was assumed at $p < 0.05$.

Results: There were no differences between the groups with respect to age, weight, intraoperative hemodynamic changes, SpO_2, respiratory rate, times to wakefulness or extubation, duration of recovery room stay, postoperative narcotics or dose of alfentanil. Group D patients had a significantly lower incidence of postoperative emesis compared with either group M or P. Although patients receiving M tended to have a lower incidence of postoperative emesis compared with placebo, this difference was not statistically significant (see table below).

Discussion: Postoperative emesis associated with opioid administration is a significant clinical problem in outpatient anesthesia because it may prolong discharge from the hospital. D and not M significantly reduced opioid-associated emesis without prolonging the duration of hospitalization.

This study was supported in part by Janssen Pharmaceutica.

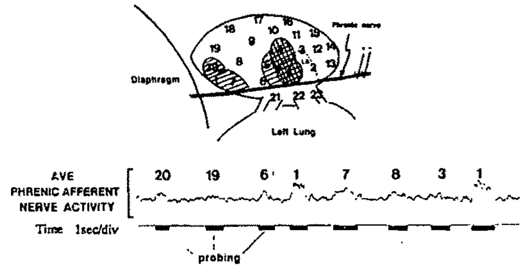
	Age (mos)	Wt (kg)	Awake (min)	Vomiting	Recovery (min)	Alfentanil (µg/kg/min)
D	55±32	19±9.7	7.4±8.6	2/16*	185±87	2.6±0.53
M	50±26	16±4.8	6.0±2.4	6/14	164±86	2.6±0.36
P	45±26	16±5.0	4.8±4.2	9/14	148±71	2.5±0.55

* Different from placebo.

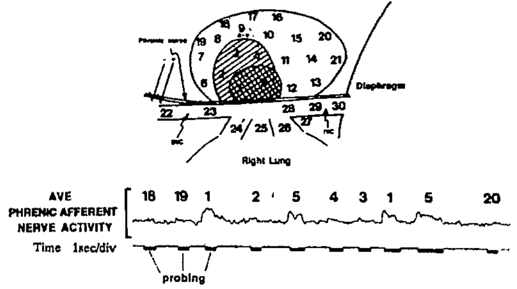
S239

CHARACTERIZATION OF PERICARDIAL MECHANORECEPTORS WITH PHRENIC AFFERENTS IN THE DOG Stephen P. Pontus, M.D. and David R. Kostreva, Ph.D. Department of Anesthesiology, Medical College of Wisconsin, the VA Medical Center and Children's Hospital of Wisconsin, Milwaukee, Wisconsin.

Pericarditis, pericardial effusion and pericardial tamponade are clinical problems that often result in life-threatening complications. One aspect of pericardial physiology that needs to be studied involves the neural influences of pericardial function. The pericardium of most mammals including man is known to have mechanoreceptors and chemoreceptors with vagal, sympathetic and phrenic afferent neurons. However, the functional role of pericardial receptors remains inadequately understood. Recent studies in our laboratory demonstrate that pericardial receptors with afferents in the phrenic nerve are very sensitive to changes in pericardial distention and touch. Mongrel dogs anesthetized with pentobarbital sodium 35 mg/kg i.v., were intubated and placed on positive-pressure ventilation. Pericardial receptors with afferent fibers in both the left and right phrenic nerves were recorded in seven dogs. These receptors were located in the pericardium overlying the A-V groove. The receptive region on the left side is shown in the figure below.



The diagonal lines represent an area of sensitivity to pericardial probing. The cross hatching represents an area extremely sensitive to touch and pressure. Bursts of afferent nerve activity are shown in the tracings of averaged nerve activity. The receptive areas on the right side are shown in the second figure.



Both the parietal and fibrous pericardium were examined using a flap of pericardium which included the phrenic innervation. The flap was probed on both surfaces to demonstrate that the receptors were in the pericardium. In addition, chemosensitivity of these receptors was tested. Capsaicin (200 µg/ml) and bradykinin (10 µg/ml) were applied to the receptive areas with flushing of the area with saline between applications. The receptors did not respond to chemical stimulation. All of the phrenic recordings were done from multifiber preparations or the whole phrenic nerve. The action potentials fired in bursts of 2-50 or more potentials with each stimulation. Most receptors were rapidly adapting. These results suggest that the phrenic afferent innervation of the pericardium is comprised of mechanoreceptors with discreet anatomical locations. These receptors may be sensitive beat to beat monitors of cardiac volume. These results are important since little is known about the characteristics and function of pericardial receptors with phrenic afferents.

S240

Title: INTUBATION CONDITIONS AFTER ADMINISTRATION OF ORG 9426 DURING NITROUS OXIDE - FENTANYL - MIDAZOLAM ANESTHESIA

Authors: D. Powers, MD, D. Lefebvre, MD, G. Knos, MD, J. Cyran, PhD, B. Brandom, MD
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Introduction: ORG 9426 is a steroidal non depolarizing muscle relaxant with an ED_{95} of 285 µg/kg in humans during balanced anesthesia.[1] Bolus administration of ORG 9426 can produce mare rapid onset of paralysis than is produced by vecuronum.[2,3] The purpose of this study was to evaluate the intubation conditions obtained.

Methods: Institutional approval was obtained and 50 ASA I or II consenting surgical patients ages 18 to 70 were studied. An initial group of 36 patients was randomly assigned to receive one of three ORG 9426 doses. Group I (450 µg/kg); Group II (600 µg/kg); Group III (750 µg/kg). Patients were premedicated with midazolam and metaclopramide or cimetidine. Anesthesia was induced with thiopental 2-6 mg/kg, fentanyl 2-6 µg/kg and midazolam 0-0.1 mg/kg IV and maintained with incremental doses of fentanyl and midazolam and 50-70% nitrous oxide in oxygen. Neuromuscular blockade was evaluated using a Datex NMT EMG. The ulnar nerve was stimulated with surface electrodes with repeated TOF stimuli (2 HZ for 0.2 m sec at 10 sec intervals). ORG 9426 was administered intravenously over 5 seconds. Intubation was initiated 60 seconds later. Intubation was characterized as excellent, good, fair, poor, based on jaw relaxation, vocal cord relaxation and gross muscular movement of extra laryngeal structures. EEMG at intubation [twitch as a % of baseline (T_1/T_c)] and time to return of EEMG to 25% of baseline (T_{25}) were recorded. Based on the results from the randomized Groups I, II, and III an optimum intubating time and dose of ORG 9426 was estimated. It appeared that onset of adequate intubating conditions was more a function of time to intubation rather than dose at the doses studied. Group IV therefore received 750 µg/kg and was intubated at 70 seconds. Statistical analysis utilized ANOVA and a contingency table.

Results: Results are expressed as mean ± SD, where appropriate, and summarized in Table 1. No statistically significant intergroup differences occurred among Groups I, II, or III. Overall intubating conditions in Group IV were excellent.

Discussion: ORG 9426 may offer superior conditions for rapid intubation compared with currently available non depolarizing relaxants. Our T_1/T_c data suggests that it may be worth while to further study intubating conditions at 70 seconds in doses lower than 750 µg/kg.

Table 1

Group	Age (years)	Wt (kg)	T_1/T_c (at intubation)	Return to T_{25} (min)	Intubation Conditions
I n=12	43±15	73±15	49±27	22±8*	3E, 7G, 2F
II n=12	42±15	74±20	50±35	36±11	7E, 4G, 1F
III n=12	41±12	71±15	42±31	35±16	5E, 7G
IV n=14	49±13	69±12	20±9	49±15	13E, 1G

* $P < 0.05$, I and II, I and III (ANOVA)

References:
1. Anesthesiology A773, Vol 71, No3A, Sept 1989
2. Anesthesiology A906, Vol 73, No3A, Sept 1990
3. Anesthesiology A890, Vol 73, No3A, Sept 1990

S241

TITLE: COMPARISON OF FLUMAZENIL AND PLACEBO ON EMERGENCE FROM A STANDARDIZED GENERAL ANESTHETIC

AUTHORS: J Pregler MD*, S Steen ScD MD, J Mirman MD
AFFILIATION: Depts of Anesthesiology, L.A. County-USC Medical Center, Los Angeles, CA and *George Washington University Medical Center, Washington, DC.

Introduction: Benzodiazepines used intraoperatively can occasionally cause prolonged sedation. Flumazenil (Anexate) is an imidazobenzodiazepine that functions as a benzodiazepine receptor antagonist. This clinical investigation was part of a multicenter study to evaluate the efficacy and safety of IV flumazenil in reversing the central effects of midazolam in a general anesthetic technique.

Methods: Thirty ASA I-III inpatients entered and completed this IRB approved study. All were interviewed preoperatively and baseline performance on a psychomotor battery of tests was obtained, which included an observer's assessment of sleep status, vital signs, responsiveness to verbal stimuli, quality of speech, facial expression, eye coordination, recognition of a picture card, finger-to-nose coordination, ambulatory function and the observer's assessment of discharge readiness from the recovery room. General anesthesia induction was performed with midazolam and fentanyl. Maintenance of anesthesia was obtained with midazolam, fentanyl and isoflurane in N2O and O2 (70:30). Muscle relaxants were given as needed and fully reversed on emergence. In the recovery room the test drug was administered IV in a double blinded, randomized manner at time 0; 20 patients received flumazenil (F), the rest placebo (P). Testing as described above was done at Time 0,5,15,30,60,120,150 and 180 minutes. On post-op day 1 patients were asked to recall the pictures they had been shown during recovery.

Results: Demographic data and drug dosages were similar for both groups. A mean composite score was assigned to each patient which included responsiveness to verbal stimuli, speech, facial expression and eye coordination. Group F had higher mean composite scores and better recognition of pictures at 5 and 15 minutes and better finger-nose coordination at 5, 15 and 30 minutes ($p<0.05$). There were no significant differences between groups at other times. On post-op day 1, no patient in either group correctly identified any of the pictures shown to them in the recovery phase, although 5 of 20 patients who received flumazenil incorrectly picked pictures that were not shown in this study.

Discussion: It was clinically evident who had received flumazenil in the first hour of recovery after general anesthesia. At later times there was no evidence of improved cognitive function.
No improvement of memory ability was demonstrated in the flumazenil group. The tendency to confabulate on follow-up interview raises legal considerations concerning early discharge of these patients.

S242

TITLE: Comparison of the onset times and intubating conditions after ORG 9426 and suxamethonium

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Introduction: Fast onset time resulting in rapid development of optimal intubating conditions is one of the highly desirable properties of the neuromuscular blocking agents. Particulary in short lasting day care surgical intervention, rapid onset and brief time course of neuromuscular blocking activity are of major importance. ORG 9426 is a new, non-depolarizing neuromuscular blocking agent with a similar duration of action as vecuronium but with a faster onset time(1). This randomized study was designed to compare the intubation conditions and the onset times after ORG 9426 and suxamethonium.

Methods: 30 consenting ASA Class I and II patients of either sex, normal at weight, between 18 and 65 years of age, without suspect or known neuromuscular disorders participated in this study. Patients were premedicated with 1 mg/kg pethidine given together with 0.01 mg/kg atropine i.m. one hour before induction. Anaesthesia was induced with propofol up to 2,5 mg/kg and alfentanil up to 25 mcg/kg. and maintained by controlled ventilation with 2:1 nitrous oxide /oxygen and continuous infusion of propofol (4 mcg/kg/h) and alfentanil (50 mcg/kg/h). Neuromuscular transmission was assessed by single twitch stimulation of the ulnar nerve at the wrist with surface electrodes and measurement of the force of the thumb adduction with a Mechanomyograph.According to the random assignment, patients, were given either 0.6 mg/kg (2x ED_{95}) of ORG 9426 or 1 mg/kg suxamethonium. Sixty seconds after administration of the single bolus of muscle relaxant each patient was intubated. Intubation conditions were scored as exellent (good jaw relaxation, vocal cords open, no response to intubation), good (good jaw relaxation, vocal cords open but minimal reaction to intubation), poor (moderate jaw relaxation, moving vocal cords, intubation requiring pressure accompanied by coughing and/or bucking) or as inadequate (intubation impossible due to poor jaw relaxation or closed cords).

Results: The response to the initial dose is shown in table 1. Unlike patients treated with ORG 9426 in the suxamethonium group one patient showed poor intubation conditions. The clinical judgement under the conditions of this study revealed better intubating conditions in the ORG 9426 treated patients , however, the difference did not reach the level of statistically significance.

Discussion: The results of this study show ORG 9426 to be the first nondepolarising neuromuscular blocking agent to challange the supremacy of suxamethonium for intubation. The intubating conditions 60 seconds after the administration of 0,6 mg/kg ORG 9426 were even better than after suxamethonium. The onset time after suxamethonium was significantly shorter than that after ORG 9426 but this difference in actual time appears to be clinically irrelevant (0,8 min vs 1,2 min). The clinical duration of action associated with the intubating dose of ORG 9426 provides adequate muscle relaxation for the duration of most of the short lasting surgical interventions. Based on the above and on the relative freedom of side effects, ORG 9426 appears to be the drug of choice for day care surgery.

table 1	onset (min)	duration 25% (min)	duration 75% (min)	recovery incex (min)
suxamethonium	0,8±0,1	8,1±2,6	10,3±3,9	2,2±1,4
ORG 9426	1,2±0,5	25,3±5,0	33,1±5,9	7,8±2,1
p<	0,01*)	0,0001*)	0,0001*)	0,0001*)

*) = highly significant

References:
1. Anasth. Analg 70:p.437 1990

S243

TITLE: NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (NCPAP) IMPROVES RESPIRATORY FUNCTION IN PATIENTS WEANED FROM MECHANICAL VENTILATION.

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INTRODUCTION: Continuous positive airway pressure (CPAP) improves pulmonary oxygen transfer by re-establishing functional residual capacity (FRC). We examined the effects of a CPAP-levels of 10 cmH2O applied via face (mask CPAP) and nose (NCPAP) masks on the change in FRC (ΔFRC) and gas exchange in ten patients after weaning from mechanical ventilation.

METHODS: Ten patients with acute lung failure (lung injury score≥ 2.5) (1), who were weaned from mechanical ventilation, extubated and breathing spontaneously for at least six hours were studied. Decreasing oxygenation indicated a demand for CPAP breathing. The continuous, high-flow CPAP circuit consisted of an air source (fraction inspiratory O2 (FiO2) = 0.21), a heated cascade humidifier and a compliant, 3-L reservoir bag in the inspiratory limb. The patient end of the system was attached to a snugly fitting face mask or nose mask . The expiratory limb ended in a water-column threshold resistor producing a positive pressure of 10 cmH2O measured at airway opening. Air flow was adjusted to minimize the pressure swing at this location. Initially all patients were breathing spontaneously at ambient pressure for control; mask CPAP and NCPAP were then applied in random order separated by a 30-minute period of breathing at ambient pressure. Thoracoabdominal motion was measured using respiratory inductive plethysmography (RIP). The changes in end-expiratory levels of the sum tracing of RIP were quantitated to asses ΔFRC (2). Comfort of mask CPAP and NCPAP were quantitated using a visual analogue scale (0=severe uncomfortable/10 = highly comfortable).

RESULTS: Both CPAP methods result in an almost identical increase of ΔFRC (NCPAP: ΔFRC = 294±82 ml; mask CPAP: ΔFRC = 290±85 ml). Arterial O2 tension (PaO2) increased significantly during mask CPAP and NCPAP at 10 cmH2O and FiO2=0.21 (TABLE 1). Arterial CO2 tension (PaCO2), tidal volume (Vt) and breathing frequency (f) were similar under both CPAP methods Two patients breathed irregulary tacking a few breaths at an elevated lung volume, followed by one deep expiration caused by mouthopening,while mask pressure hardly changed. The patients rated NCPAP (8.6±0.9) significantly more comfortable than mask CPAP (2.6±0.8).

DISCUSSION: Our study indicates that the major advantages of CPAP, the improvement of FRC and oxygen transfer, can also be achieved with NCPAP during the weaning from mechanical ventilation after acute lung failure. Moreover, our patients prefered NCPAP to mask CPAP, rendering nose mask suitable for long-term CPAP therapy.

TABLE 1:

	Control	Mask-CPAP	NCPAP
PaO2 (mmHG)	59±11	69±11*	71±10*
PaCO2(mmHG)	32±5	33±4	33±4
Vt (ml)	385±90	390±110	400±107
f (b/min)	29±2	26±2*	26±2*

*p≤.05 compared to control

References:
1. Murray JF,et al. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720-723.
2. Benjamin RG,et al.. Removal of bronchial secretion by two-phase gas-liquid trasport. Chest 1989; 95:658-663.

S244

Title: EFFECT OF PATIENT POSITION ON THE INCIDENCE OF VASOVAGAL RESPONSE TO VENOUS CANNULATION

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Introduction: Vasovagal syncope can occur in individuals under stressful circumstances, including venous cannulation (VC).[1] This study was undertaken to determine the effect of position (sitting [St] or recumbent [Re]) on the incidence of fainting (F) or near-fainting (NF) in ambulatory surgical patients undergoing VC. Potential predisposing factors, and the hemodynamic responses to cannulation were recorded.

Methods: Institutional review board approval was obtained to observe the effect of St versus Re position of VC in surgical outpatients. Three hundred unpremedicated outpatients, age ≤40 years, were randomized by week to the St or Re position. Baseline mean arterial pressure (MAP) and heart rate (HR) were recorded in a preoperative clinic, and 1 minute before, during, and for 6 minutes after VC while a trained observer recorded signs or symptoms suggestive of a vasovagal attack. Patients were considered symptomatic if reporting dizziness, hot, cold, sweaty, nauseated feelings or demonstrated shivering, vomiting, pallor or unconsciousness. Continuously distributed variables are presented as mean (± standard deviation, SD) Between treatment differences are tested by unpaired *t*-test. Differences in proportions were assessed by chi-square tests. Multivariate assessment of relative risk of prognostic variables was by logistic regression.

Results: Twenty-three St patients (12.6%) experienced vasovagal symptoms; 2 St patients (1.3%) had syncope. All patients recovered quickly without sequelae. Patient position (p < .002) and a history of fainting (p < .001) combined were positively correlated with the incidence of vasovagal response to VC. In symptomatic patients (F + NF), MAP fell from 89.4 (± 13.5) to 65.8 (± 14.0) mmHg in sitting patients and from 93.0 (± 21.1) to 64.0 (± 15.4) mmHg in recumbent patients.

Conclusion: F or NF occurs more frequently in the sitting than in the recumbent position. Based on our data, the recumbent position is recommended in unpremedicated outpatients, especially those with a history of fainting who have an 8 times greater risk of F or NF.

Reference: 1. Anesthesia Review 15 (Mar/Apr):13-16, 1988.

Table 1. Demographics and Symptoms (mean ± SD, or %)

	Sitting	Recumbent
n	159	141
Age (years)	30.2 (6.6)	30.0 (6.5)
Females (%)	60.4	56.7
Fasting Time (hrs)	10.4(3.4)	10.2(3.3)
Baseline MAP (mmHg)	89.4 (11.5)	87.4 (10.6)
Hx§ of Fainting (%)	10.7	10.6
% Symptomatic (NF & F)	12.6*	2.1
Near Faints (%)	11.3**	2.1
Faints (%)	1.3	0
% Symptomatic (NF & F) with:		
Hx§ of fainting (%)	41	13
No hx§ of fainting (%)	9	1

* p < .001
** p < .004
§ Hx = History

S245

TITLE: ANALGESIC DOSING PATTERNS IN PEDIATRIC PATIENTS AFTER OPEN HEART SURGERY

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Introduction: Inadequacy of pediatric pain therapy is often blamed on fears of addiction, potential for respiratory depression especially in infants, possible exacerbation of cardiovascular instability in the acute patient and difficulties in objectively reporting pain. This study was undertaken to determine analgesic dosing patterns after open heart surgery in the Pediatric Intensive Care Unit (PICU). Only patients with median sternotomy incisions were included so that the operative pain stimulus remained fairly uniform. All patients were intubated and ventilator dependent upon admission to the PICU.

Methods: Institutional approval was obtained for the retrospective analysis of 78 consecutive pediatric patients. A standard data sheet was used to record drug doses and times, demographic data, and clinical information. Study periods were defined as the first 12° hrs after PICU admission, and post-operative (POD) days 1,2, and 3. Patients were divided into three groups to define postoperative condition: Group I, stable, requiring no inotropic support; Group II, stable, but with one vasoactive infusion; and Group III, unstable, with multiple infusions. Standard morphine dose (SMD) was defined as 0.1 mg/kg q3° as ordered on the preprinted PICU admission order sheets. Data were analyzed using analysis of variance and student t-test. $P<0.05$ is considered significant.

Results: Mean age was 36 months ± 44.3; mean weight was 13 kg±12.6. The mean morphine (MS) dose received in the first 12° closely paralleled the SMD($p=0.194$). After the first 12°, the number of patients receiving MS and the actual dose given fell rapidly over time (Table I). No dosing variability existed between age groups or postoperative condition ($p=0.3$). Sixty-six patients (85%) were extubated in the first 24°. Although MS doses while intubated approximated the SMD, narcotic doses dropped >66% immediately after extubation in all age groups. Furthermore, the mean total narcotic dose for the 3 day study period was 1.6±3.8 mg/kg, significantly lower than the potential 2.8 mg/kg ($p=.0001$) that patients could have received had the SMD been followed. Despite the low dose actually given, 96% of the patients had documentation in nursing notes of pain, crying or agitation.

Conclusions:

1. In the first 12° after ICU admission, MS dose received did not deviate from a standard dosing regimen, even though patients were intubated and protected from respiratory depression had titration to effect been attempted.
2. Fear of respiratory depression in the extubated patient probably limited the amount of narcotic given, even in the ICU setting with extensive monitoring and observation.
3. Despite concerns about overdosage in sick or very young children, no variability in dosing patterns was evident for these groups.
4. In the first 72° postop open heart surgery, overall MS doses are very low despite nursing documentation of pain and agitation.

MS DOSE RECEIVED vs SMD (.4 mg/12°)

	N=# Pts Receiving MS	Dose (mg/kg)	P
First 12°	78	.45	0.194
Day 1	68	.26	0.0001
Day 2	38	.09	0.0001
Day 3	13	.05	0.0001

S246

Title: TORADOL ANTAGONIZES CLONIDINE-INDUCED ANTINOCICEPTION IN RATS

Authors: A.K. Rattan, Ph.D., J.S. McDonald, M.D., K.L. Koo, B.S., G.A. Tejwani, Ph.D.
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Toradol (ketorolac tromethamine), the first potent, short acting injectable nonsteroidal, anti-inflammatory analgesic drug is now available in the United States. Clonidine, first introduced for its antihypertensive effect, has also been found to have significant analgesic activity, when administered by different routes in animals[1]. The influence of toradol on the antinociception effects of clonidine was studied using tail-flick (TF) and hot-plate (HP) tests in rats after intrathecal injections.

Male Sprague-Dawley rats (300-350 g) were anesthetized with ketamine (80 mg/kg, im) and xylazine (8 mg/kg, im) and placed into stereotaxic apparatus. A polyethylene tube (PE 10) was inserted through a slit in the cisternal membrane about 8.5 cm down the spinal subarachnoid space to the rostral aspect of the lumbar enlargement according to the method described earlier[2]. The catheter was fixed to the skull by cranioplastic cement and the animals were allowed to recover for at least a week. Antinociception was measured by using the graded stimulus TF test. A maximum stimulus of 10 sec was used to avoid skin damage. The HP test involved keeping the rat on a metal plate surface maintained at 52°C. In the absence of response animals were removed from the plate after 60 sec. Rats were injected with drugs in a volume of 10 µl followed by 5 µl of saline to flush the catheter. Data were expressed as maximum possible effect (MPE). Statistical analysis were performed by Newman Keuls 't' test.

Clonidine (1-30 µg) induced a dose-dependant increase in antinociception in both tests (TF and HP). Toradol (150-600 µg) increased the antinociception by 50-60% only at high doses in TF test only. Toradol (10 µg) decreased clonidine (10 µg)-induced antinociception from 69.1 ± 7.8 to 23.5 ± 1.61 ($p<0.05$) in TF test and 35.7 ± 4.7 to 4.5 ± 0.11 ($p<0.05$) in HP test. This antagonism was also noticed when 30 µg toradol was given in presence of 30 µg of clonidine. Naloxone (100 µg) did not affect the basal nociceptive motor response of animals but abolished antinociception produced by clonidine or toradol in both the tests (TF and HP).

In conclusion, for the first time we report that toradol decreases clonidine induced antinociception in two different analgesic tests in an animal model. This interaction between toradol and clonidine should be taken into account when these two drugs are given together clinically. As naloxone significantly decreased the antinociceptive activity of clonidine and toradol it is concluded that these drugs might act in part by causing the release of endogenous opioids.

References

1. Anesthesia and Analgesia 60:185-191, 1989.
2. Anesthesia and Analgesia (in press).

S247

TITLE: TRANSDERMAL FENTANYL FOR POSTOPERATIVE PAIN IN THE CHOLECYSTECTOMY PATIENT

AUTHORS: D Reinhart MD, L Carter MD, T Tyson MD, K Hagberg MD, R Mullins MD, AH Giesecke Jr MD

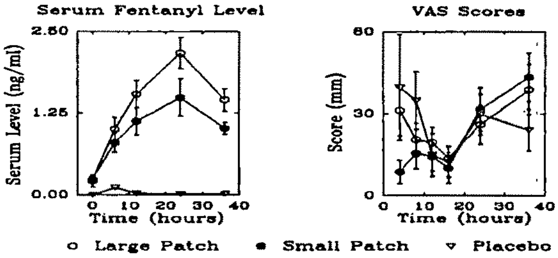
AFFILIATION: Zale-Lipshy University Hospital UT Southwestern Medical Center, Dallas, Texas

INTRODUCTION: This study, part of a multi-center investigation, was undertaken to determine safety and efficacy of Cygnus Transdermal Fentanyl in post-cholecystectomy patients.

METHODS: After Institutional Review Board approval, 55 ASA 1 or 2 cholecystectomy patients were consented and randomized to one of three groups: Group L (n=19) received a large (60 cm^2) patch delivering 90-100 µg/hr, groups S (n=19) received a small (40 cm^2) patch at 40-60 µg/hr and group P (n=17) received a placebo patch preoperatively. Postoperatively, patients in the placebo group were allowed to have intermittent scheduled IM injections of morphine sulfate, 150 µg/kg every 6 hours. Patients in group L and S (active patch) received placebo injections. Patches remained in place for 24 hours. Serum fentanyl levels were monitored. Subjects were monitored for respiratory rate, SpO2 and other adverse events. Pain (100mm visual analog and verbal scales), comfort and sedation scores were collected for the three groups.

RESULTS: Of the patients that completed the study, there was no difference (p>0.1) with respect to sedation, comfort, pain intensity, pain relief, physician or patient global assessment, visual or verbal analog scale scores. There was also no significant difference among the groups in the incidence of vomiting, decreased SpO$_2$, or decreased respiratory rate. There was a significantly higher incidence of nausea in group L with respect to the group S but not to group P. There was a significantly higher incidence of pruritus in group L (P<.05) than in group S and P. The number of patients discontinued from the study due to inadequate pain relief was significantly higher (p<.05) for the placebo group.

Adverse Event	Group L	Group S	Group P
Nausea	12(63%)	6(32%)	8(47%)
Pruritus	5(26%)	2(11%)	0(0%)
Inadequate Analgesia	0(0%)	2(11%)	4(24%)



CONCLUSION: In this study, transdermal fentanyl decreased the incidence of inadequate pain relief in the postoperative patient over the use of I.M. injections of morphine.

S248

TITLE: EFFECT OF KETOROLAC ON COAGULATION AS EVALUATED BY THROMBOELASTOGRAPH

AUTHORS:D REINHART,MD,T LATSON,MD,K KLEIN,MD, C WHITTEN,MD,M PATEL,BS

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INTRODUCTION: Ketorolac, a potent NSAID, is employed perioperatively as an opiate-sparing analgesic.[1] While studies have shown no increase in postoperative blood loss with the use of ketorolac for postoperative pain, others have shown that a single oral dose of ketorolac can prolong the template bleeding time by 1.3-1.7 times baseline values in healthy volunteers.[2] Concerns remain about its effect on coagulation in the peri-operative period. This study investigates the effect of ketorolac on coagulation using the thrombelastograph (TEG). The TEG reflects the interaction of coagulation precursors, and is a sensitive tool in detecting perioperative bleeding disorders.[3] The TEG measures the time course of clot formation and viscoelastic clot strength.

METHODS: Following IRB approval and informed consent, 12 healthy volunteers and 10 ASA I or II surgical patients not on anticoagulant or anti-platelet therapy undergoing superficial procedures were studied. After drawing a baseline blood sample for TEG analysis, the volunteers received 60mg ketorolac IM. One hour later, at peak serum levels, a blood sample was taken for comparision to baseline. The ten surgical patients received a standard anesthetic. Ten minutes after incision, a sample of blood was taken for baseline TEG and 60 mg of ketorolac IM was then given. One hour later, a blood sample was taken for comparision to the baseline TEG. The pre- and post- ketorolac TEGs were analyzed for changes in the R time, RK time, MA, and angle using the described method.[4] Statistical significance was assessed using a two sample t-test.

RESULTS: There was no statistically significant difference in any of the measured TEG parameters following ketorolac administration in either the surgical or healthy volunteer groups.

CONCLUSION: The overall results show that ketorolac does not cause statistically significant changes in TEG parameters. No individual patient showed evidence of significant hypocoagulable changes following ketorolac administration. We conclude that single dose IM ketorolac given intraoperatively or to healthy volunteers does not cause a hypocoagulable state as determined by TEG.

REFERENCES:

1. GWA Gilles, Anesth,1987,42:727-731.
2. K Spowart, Thromb Haemost,1988,60:382-286.
3. J Frieberger, Prob in Anesth,1987,1,No 2.
4. YG Kang, Anesth and Analg,1985,64:888-896.

S249

TITLE: EFFECTS OF POSTOPERATIVE KETOROLAC ON COAGULATION AS EVALUATED BY THROMBOELASTOGRAPH

AUTHORS: D REINHART MD, T LATSON MD, K KLEIN MD, C WHITTEN MD, M PATEL BS

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INTRODUCTION: Ketorolac, a potent NSAID, is employed perioperatively as an opiate-sparing analgesic.[1] While studies have shown no increase in postoperative blood loss with the use of ketorolac for postoperative pain, others have shown that a single oral dose of ketorolac can prolong the template bleeding times by 1.3-1.7 times baseline values in healthy volunteers.[2] Concerns remain about its effect on coagulation in the peri-operative period. This study investigates the effect of ketorolac on coagulation using the thrombelastograph (TEG). The TEG reflects the interaction of coagulation precursors, and is a sensitive tool in detecting perioperative bleeding disorders.[3] The TEG measures the time course of clot formation and viscoelastic clot strength.

METHODS: Following IRB approval and informed consent, 12 healthy volunteers and 10 ASA I or II surgical patients not on anticoagulant or antiplatelet therapy undergoing superficial procedures were studied. After drawing a baseline blood sample for TEG analysis, the volunteers received 60mg ketorolac IM. One hour later, at peak serum levels, a blood sample was taken for comparision to the baseline. Upon arrival to recovery room, ten surgical patients had a blood sample taken for baseline TEG and 60mg ketorolac IM was then given. One hour later, a blood sample was taken for comparision to the baseline TEG. The pre- and post-ketorolac TEGs were analyzed for changes in the R time, RK time, MA, and angle using the described method.[4] Statistical significance was assessed using a two sample t-test.

RESULTS: There was no statistically significant difference in any of the measured TEG parameters following ketorolac administration in either the surgical or healthy volunteer groups.

CONCLUSION The overall results show that ketorolac does not cause statistically significant changes in TEG parameters. No individual patient showed evidence of significant hypocoagulable changes following ketorolac administration. We conclude that single dose IM ketorolac given post-operatively or to healthy volunteers does not cause a hypocoagulable state in the surgical patient as determined by TEG.

REFERENCES:
1. GWA Gilles, Anesth,1987,42:727-731.
2. K Spowart, Thromb Haemost,1988,60,382-286.
3. J Frieberger, Prob in Anesth,1987,1:No 2.
4. YG Kang, Anesth and Analg,1985,64,888-896.

S250

TITLE: TRANSDERMAL FENTANYL FOR POSTOPERATIVE PAIN IN THE ORTHOPEDIC PATIENT

AUTHORS: D Reinhart MD, R Mullins MD, K Hagberg MD, N Watson MD, H Raja BS

AFFILIATION: UT Southwestern Medical Center Dept of Anesthesiology, Dallas, Texas

INTRODUCTION: This study, part of a multi-center investigation, was undertaken to determine the safety and efficacy of Cygnus Transdermal Fentanyl for postoperative pain in patients undergoing lower extremity orthopedic procedures.

METHODS: After Institutional Review Board approval, 21 ASA 1 or 2 orthopedic patients were consented and randomized to one of three groups: Group L received a large (60 cm^2) patch delivering 80-100 μg/hr of fentanyl, group S received a small (40 cm^2) patch delivering 40-60 μg/hr and group P received a placebo patch. Patches were placed 1 to 2 hours preoperatively. Postoperatively, patients in the placebo group were given intermittent IM morphine, 150 μg every 6 hours. Patches remained in place for 24 hours. Subjects were monitored for respiratory rate, SpO_2 and other adverse events. Pain (100mm visual analog scale and verbal scales), Comfort and sedation scores were obtained for 36 hours.

RESULTS: A significant number of patients from each group failed to complete the protocol due to inadequate pain relief. Among the patients that completed the study, there were no statistically significant differences in pain relief, pain intensity, comfort, sedation, physician global assessment or patient global assessment scores.
The number of patients discontinued from the study due to inadequate pain relief were: Group L, 3/7(43%); Group S, 4/8(50%), Group P, 3/6(50%).

CONCLUSION: Transdermal fentanyl delivered at a rate of 40-60μg/hr or 90-100μg/hr did not decrease the attrition rate due to inadequate analgesia in lower extremity orthopedic patients in this study.

S251

Title: COMPARISON OF 4 METHODS OF MEASURING REGIONAL MYOCARDIAL FUNCTION DURING ADJACENT ISCHEMIA IN THE DOG

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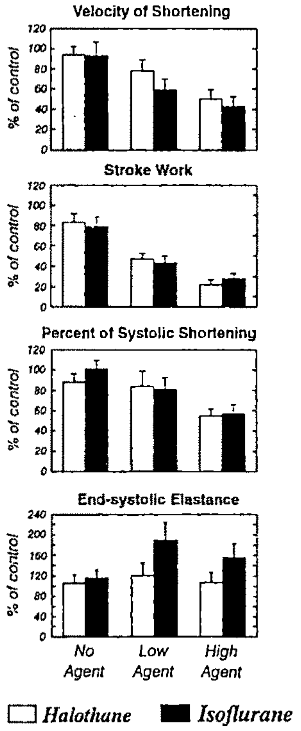
Introduction/Methods: During acute myocardial ischemia, function of the remaining, non-ischemic muscle is the primary determinant of residual cardiac performance. We compared 4 methods of measuring regional myocardial function in the normal heart muscle in 16 dogs made ischemic below the 2nd diagonal branch of the LAD. Preparation under fentanyl anesthesia included left ventricular micromanometers, regional sonomicrometer transducers over the normal and ischemic myocardium, caval occluders, LA, PA, venous and arterial catheters. Microspheres measured regional blood flow and regional myocardia $M\dot{V}_{O2}$ was calculated from A-V O_2 content differences. For comparison, either 0.5 or 1.5 MAC halothane or isoflurane was given randomly and end-systolic elastance (E_{es}), percent systolic shortening (%SS), velocity of muscle shortening (dL/dt) and regional stroke work (RSW) were calculated by computer as measures of regional myocardial function from the pressure-dimension loops of the normal myocardium. Results were analyzed by ANOVA. **Results:** The figure illustrates the effects of contiguous ischemia (No Agent) and two concentrations of anesthetic agent on the 4 methods of measuring function. dL/dt, RSW, and %SS showed little change with contiguous ischemia, but demonstrated a progressive, significant ($p < 0.05$) decrease in values with increasing concentration of either agent. There was no difference between agents. Conversely, E_{es} values rose significantly with increasing isoflurane. With both agents $M\dot{V}_{O2}$ decreased significantly by the high agent concentration. **Discussion:** The description of global myocardial function during ischemia by E_{es} is controversial[1] and our study demonstrates that regional function likewise is poorly represented by E_{es}. With little difference between agents in the fall in $M\dot{V}_{O2}$, it is doubtful that regional function increased markedly with isoflurane as depicted by E_{es}. %SS, dL/dt, and RSW appear to be more useful alternatives for its measurement.

1. Circ 80:1783-1794,1989.



S252

TITLE: DOXACURIUM BLOCK IS NOT INFLUENCED BY AGE

AUTHORS: G. Rolly, M.D.,Ph.D., J.C. De Mey, M.D.

AFFILIATION: Dept. of Anesthesia, University Hospital, Ghent (Belgium)

INTRODUCTION: Doxacurium (Dox) is a potent, long acting neuromuscular blocking agent. The purpose of this study is to evaluate its efficacy,hemodynamic effects and ease of reversal in elderly surgical patients,compared to a control group of younger adult patients.

PATIENTS AND METHODS: After approval by the ethical committee of the University Hospital, 30 informed patients, aged 18 to 64 years (Y) and 30 aged > 64 years (E) entered the study. All were male or non pregnant female ASA I or II patients, to undergo elective ophthalmological surgery for more than 2 hours.Premedication consisted of diazepam 10 mg orally. Anesthesia was induced with fentanyl 0.1 mg and propofol 2 mg/kg I.V. and continued with isoflurane 0.5-1 %, N_2O/O_2 (F_IO_2=0.33) by mask. After determination of supramaximal stimulation (TOF stimulation Datex Relaxograph) of the ulnar nerve, 40 µg/kg Dox was given; 4' later intubation was performed and T_1depression recorded. Anesthesia was continued with 1-1.5 % isoflurane in N_2O/O_2 (F_IO_2=0.33)and controlled ventilation (Pet CO_2 32-39 mm Hg). Time to 25, 50, 75, 90 % and maximal block was recorded, as well as time to 5, 10 and 25 % recovery. If necessary, Dox 5 µg/kg was given to prolong muscular relaxation. At the end of surgery the patients received neostigmine 50 µg/kg with either glycopyrrolate 10 µg/kg or atropine 20 µg/kg.

RESULTS:Height,weight and baseline heart rate were similar in Y and E; baseline syst. and diast. BP were higher in E (p<0.005). Time to onset of blockade and to maximum blockade (table) were identical (NS) in Y and E, as well as time to spontaneous recovery to 5, 10 and 25 %.

	Time (min) to blockade (Mean ± SD)					Max. block. %
	25 %	50 %	75 %	90 %	Max.	
Y n=30	3.55 ±1.59	4.87 ±2.19	7.00 ±4.56	8.96 ±4.20	20.30 ±11.70	95.10 ± 5.49
E n=30	3.47 ±1.25	4.73 ±1.39	6.37 ±1.81	9.59 ±4.98	19.30 ±12.19	97.27 ± 3.15

Two, 4 and 10' after Dox, syst. and diast. BP significantly (p<0.001) decreased (initial decrease more pronounced in E : p<0.01). Heart rate did not change (values higher in Y : p<0.01).

Duration of neuromuscular blockade till antagonisation lasted 166±41 (Y) and 170±47 min (E) (diff. NS). At that moment T_1 was 23.5±7.1 (Y) and 22.8±6.2 % (E). After neostigmine T_1 increased to 50 % after 4.0±3.8 (Y) and 5.8±4.1 min (E), and to 75 % after 10.3±9.7 (Y) and 9.4±6.6 min (E) (diff.NS). Antagonisation of Dox was juged not fast enough in 19 Y and 18 E patients, necessitating an additional dose of neostigne.

DISCUSSION: This study shows that after Dox 40 µg/kg, onset, duration and intensity of block, as well as reversal by neostigmine, were not influenced by age. Hemodynamic changes were very moderate.

S253

TITLE: METHANE ACCUMULATION DURING CLOSED CIRCUIT ANESTHESIA

AUTHORS: G. Rolly, M.D.,Ph.D., L. Versichelen, M.D.

AFFILIATION: Dept. of Anesthesia, University Hospital, Ghent (Belgium)

INTRODUCTION: When routinely using the closed circuit Physioflex^R apparatus in clinical practice for ventilating patients with an O_2/air mixture during total intravenous anesthesia (TIVA), we noticed that the inbuilt I.R. analyser indicated unexpected values for halothane. It is already reported that during closed circuit conditions methane can be present in the breathing gases (1).

It was therefore the aim of the present study to: 1/ measure if any methane was present and if so to assess the rate of accumulation with time; 2/ determine how methane was influencing the I.R. read out of potent inhalation anesthetic vapor concentration.

PATIENTS AND METHODS: As soon as the dial indication for halothane vapor concentration, measured by I.R. technique (3.3 µm wavelength), exceeded 0.2 % during TIVA administration (propofol and fentanyl) patients were included in the study. It concerns 10 ASA I or II informed patients, anesthetised for gynecological laparoscopy with CO_2 insufflation. At the end of the ventilation with an O_2/air mixture given in true closed circuit conditions, 1 liter of breathing gases was sampled at the Y piece located at the endotracheal tube connector and fed into a vacuum bottle. The gases were subsequently analysed for the presence of methane gas, by means of gas chromatography (flame-ionisation detection).

RESULTS: Methane gas could be traced in all gas samples of the 10 patients. Mean concentration was 861 ppm (range 139 and 1967 ppm) after a mean closed circuit anesthesia time lasting 78 min (range 43 and 150 min). The calculated average accumulation was 703 ppm/hour. The halothane indication at the anesthetic concentration window of the Physioflex apparatus at the time of gas sampling was on average 1.0 % (range 0.3 and 2.0 %). The ratio of methane ppm/vapour % indication was 801 (range 646 and 1187).

DISCUSSION: The present study confirms that during closed circuit conditions methane accumulates in the breathing gases in some patients. The concentration measured was however much higher than mentioned previously; in the present study however true closed circuit conditions were maintained during the entire anesthetic period, as successive requests for system flush (as asked by the program every 30 min) were deliberately ignored. No other foreign gases were searched for, so it is impossible to determine their eventual contribution to the recorded anesthetic vapor concentration. The analysis of anesthetic vapor concentrations by I.R. absorption at a wavelength of 3.3 µm is clearly disturbed by the presence of these foreign gases. During closed circuit conditions this has to be taken into account or alternate measuring techniques have to be used. Therefore the computer controlled halothane administration based on I.R. analysis, used in Physioflex^R apparatus, has to be questioned.

REFERENCE:

1. Anesth. Analg. 64; 343: 1985.

S254

TITLE: MODERN AUTOMATIC CLOSED CIRCUIT ANESTHESIA IS NOW POSSIBLE

AUTHORS: G. Rolly, M.D.,Ph.D., L. Versichelen,M.D.

AFFILIATION: Dept. of Anesthesia, University Hospital, Ghent (Belgium)

INTRODUCTION: The newly developed Physioflex^R (Physio-The Netherlands) apparatus is a valveless closed circuit system, with an inbuilt blower, rotating the gases unidirectionally in the circuit (70 l/min). Four membrane chambers are built in the circuit, for controlled ventilation purposes and/or sensing the respiratory movements. Computer controlled injection of small quanta of oxygen and nitrous oxide (or air) are done and excess gases are eventually evacuated. Inspiratory oxygen concentration is continuously measured by a paramagnetic oxygen sensor and CO_2, N_2O and volatile anesthetics are measured by infrared inbuilt spectrometry. Liquid anesthetic is injected by computer controlled syringe administration. Volatile anesthetic concentration (Fet anesth.) is lowered by automatic opening of a charcoal cannister.

It was the aim of the present study to assess the following claimed features of this system :
1. automatic constancy of the dialed F_IO_2;
2. automatic constancy of the dialed Fet anesth.;
3. anesthetic washout (in closed circuit conditions).

The study was approved by the ethical committee of the University Hospital and Physioflex^R is routinely used in our clinical praxis since 1 year.

METHODS: After anesthesia induction (propofol, fentanyl, vecuronium) and intubation 25 ASA I or II informed patients were connected to a Physioflex^R. According to clinical needs an O_2/N_2O mixture was choosen (F_IO_2 0.3-0.5). The isoflurane (or halothane) concentration was dialed and adapted according to the patients' individual needs. Respiratory gases were continuously sampled (120 ml/min) at the Y piece of the breathing circuit and analysed with a Centronic quadrupole mass spectrometer.

RESULTS:
1. During steady state conditions, F_IO_2 was stable at the set value. After dial changes, the new concentration was obtained within 40 seconds.
2. Minor changes in Fet anesth. occured, while F_I anesth. showed larger fluctuations (due to the computer programmed syringe injection of liquid anesthetics).
3. The decrease of Fet anesth. to a new value, or complete washout by charcoal, were very rapid (decrease of F_I anesth. to zero within 10 sec). Washout of N_2O in closed circuit conditions was much slower (8-10 min).

DISCUSSION: This computer controlled closed circuit anesthesia machine (respirator) fulfils the requirements of modern anesthesia practice. Fast adjustment and constancy of the O_2 concentration after dial changes are the main features. The N_2O concentration decreases slowly by N_2 excretion out of the body tissues during true closed circuit conditions, and can be restored by temporarily activating a flush program. Fet anesth. is stable and can be quickly altered in both directions during closed circuit conditions. Washout of N_2O is however slow.

S255

Title: Can Preoperative Naproxen Sodium Reduce Postoperative Pain in Arthroscopic Knee Surgery?
Authors: ME Rooney, BSP; WE Code, MD, PM Browne, BSc; T Hertz; DJ Liepert, MD, RW Yip, MD
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Introduction: Arthroscopic surgery is a common orthopedic procedure, and its advantages include: less pain, shorter hospitalization, and quicker rehabilitation.[1] Previous studies have suggested that NSAIDS (non-steroidal anti-inflammatory drugs) may decrease the inflammatory component of the arthroscopic procedure, and thus both reduce pain and speed recovery.[2,3] However, these studies evaluated the effectiveness of NSAIDS administered postoperatively in multiple doses. This study was therefore undertaken to assess the efficacy of a single preoperative dose of NSAID administration.

Methods: All ASA I and II patients scheduled for arthroscopic knee surgery were considered for study. Consenting patients were randomized in a double blind manner to receive either 550mg of naproxen sodium or a placebo 1 to 2 hours prior to surgery. No other premedicant was given and local or general anaesthesia was determined by patient and/or anaesthetist personal preference. Patients marked a visual analogue pain scale preoperatively and again following the procedure. Chi-squared tests and Wilcoxon rank sum test were used for statistical comparison of the groups, with $p<0.05$ considered significant.

Results: There was no significant difference between the groups in terms of age, sex, weight, use of opioids during anaesthesia, or baseline pain scores. 21 patients received naproxen sodium, and 28 patients received placebo.

In patients receiving 550mg naproxen sodium, there was a significant decrease in pain scores reported (means ± SD) postoperatively at one hour (0.9±1.7 for drug (n=21) vs: 2.0±2.0 for placebo n=28), and in scores reported at 100 minutes postoperatively (0.9±1.7 for drug (n=17) vs: 2.0±2.0 (n=25) for placebo). There was also a significant decrease in the pain scores reported 24 hours postoperatively (0.8-±2.0 for drug (n=19) vs: 3.0±2.9 for placebo (n=22).

Discussion: Our results show that treatment with 550mg of naproxen sodium 1-2 hours preoperatively can significantly reduce postoperative pain in arthroscopic knee surgery.

References: 1. Clin Sport Med 1985; 4: 279. 2. J Bone Joint Surg 1985; 67: 567. 3. Clin Ther 1986; 8: 164.

S256

TITLE: ORAL SEDATION OF INFANTS AND CHILDREN IN THE ICU: A PHARMACOKINETIC AND PHARMACODYNAMIC STUDY
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Introduction: The ability of the ill child to cooperate with the medical therapy used in their treatment may directly effect the outcome. Sedative medications are often used in the young child who is unable to comprehend the need to lay still. The ability to provide continuous intravenous sedation may be limited by inadequate or absent venous access. In long term care many of these children have functioning alimentary systems and can receive nutrition and medications via this route. The purpose of this study was to investigate the use of oral midazolam for continuous sedation in the Pediatric Intensive Care unit, and to determine the effects of feeding on midazolam plasma concentration.

Methods: This study received approval of the institutional review board for studies involving human subjects. Children age 1 month to 4 years were entered into the study if they were taking oral feeds, had no liver disease or taking no medication which induced hepatic microsomal enzymes, and needed to be sedated. Children were given a loading dose of midazolam 0.75 mg/kg orally or down their nasogastric tube. This was followed by midazolam 0.5 mg/kg every three hours. The patient's level of sedation was rated using a 6 point scoring system every 15 minutes for the first 90 minutes and then hourly for the duration of the study (24-48 hours). This sedation scoring system rated sedation using a 2 part scoring system (behavior and physiologic). On the behavioral scale, a comatose child was rated as a 0, a calm child as a 3, and a wild child as a 5. On the physiologic score, a child received a score of "B" for baseline values and a score of "A" for physiologic values <10% below normal or a "C" for values 10% above normal. After the patient had received at least 4 doses, the patient was randomized to receive midazolam 15 minutes before feeds or 15 minutes after feeds. Heparinized samples were taken before the midazolam dose and then the following intervals after the medication: 10,20,30,60,90,120, and 180 minutes. The patient then received the midazolam dose in the other relationship to feeds and blood samples were obtained as before. The plasma was separated and the samples were frozen until analyzed by HPLC.

Results: Trained observers rated sedation in the seven patients studied as a "5" less than 4% of the time. The majority of time (64%) patients were rated a 1 or 2 on the behavioral sedation scoring system. The physiologic portion of the sedation score was rated as "B" >95% of the time. There were trends of sedation scores and plasma levels in individual patients, but analysis of the sedation scores and the plasma level demonstrated no correlation between the two (r2 =0.008). The plasma midazolam concentrations were significantly higher when the midazolam was given after feeds then before feeds. ($p<0.01$)

Discussion: In those patients with functioning alimentary systems oral midazolam may be used to keep children continuously sedated in the ICU setting. Midazolam plasma concentration will be higher if the drug is given after feeding than before feeding, but a specific plasma midazolam level did not correlate with a level of sedation. Individual patients tended to become more sedated when the plasma midazolam was higher. If the sedation score of 3 is considered optimal this could be best achieved by decreasing the bolus dose followed by a more frequent administration of the subsequent dose. The oral midazolam was well tolerated and no side effects were noted.

S257

TITLE: CONTAMINATION OF SINGLE DOSE OF BUPIVACAINE VIALS USED REPEATEDLY IN THE SAME PATIENT

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Introduction. Continuous lumbar epidural anesthesia is the most popular anesthetic technique for the laboring parturient with bupivacaine (BUP) being the most commonly used local anesthetic. BUP is supplied in preservative-free single dose 30 cc vials. Common practice is to draw the entire 30 cc of BUP into one syringe and to use that syringe exclusively with one patient. Throughout the first and second stages of labor, additional BUP often needs to be administered every 90-120 minutes to maintain adequate analgesia. With each administration, the cap is removed from the epidural catheter and the syringe is attached to deliver the additional BUP. Although every effort is made to maintain aseptic conditions during the procedure, it is possible that the BUP syringe could harbor contaminant growth. This study determined that the syringe contents becomes contaminated with bacterial growth when it is repeatedly used over several hours.

Methods. Institutional Research Review Board approval was secured and the subjects were laboring parturients who elected to have epidural anesthesia. The contents of two 30 cc vials of bupivacaine (0.25%) were drawn up, each into its own 25 cc syringe. One syringe served as a control and the second was used to administer the initial and repeated doses of BUP to the same patient. After each administration, a sample from the patient syringe and the control was taken to be cultured. Samples were incubated at 37°C for a minimum of 8 days.

Results. Data have shown that of the samples taken from 18 patients, those of 6 patients had bacterial growth. One of the controls also had bacterial growth. No patient demonstrated any clinical signs or symptoms consistent with infection. Most of the bacteria were those found on the skin. One sample, however, showed a high bacterial count consistent with nasal flora.

Discussion. Others have reported a 5 % incidence of contamination for the same 10 cc plastic syringes which were reused on the same patients for local anesthesia administration (1). Those syringes were cultured after delivery, not after each epidural injection as was done in the present study. In another study, at least 50% of the plastic and 100% of glass syringes can be contaminated when used more than once (2). The data of this study is in accordance with the findings of these earlier investigations.

References.

1. James FM, George RH, Naiem H, White GJ: Anesth Analg 55:187-190, 1976
2. CE. Bloggs, MAE Ramsay, JD Jarvis: Br J Anaesth 46:260-262, 1974

S258

ESMOLOL OR SODIUM NITROPRUSSIDE IN THORACIC AORTIC CROSS CLAMP IN DOGS

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INTRODUCTION:

Paraplegia is a major postoperative complication following thoracic aortic cross clamp. Spinal cord perfusion pressure, defined as mean distal aortic pressure less the cerebrospinal fluid pressure, has been demonstrated as one of the determining factors of spinal cord integrity during cross clamp. Sodium nitroprusside reduces spinal cord perfusion pressure by reducing distal aortic pressure. Esmolol, a beta adrenoreceptor blocker has a similar pharmacokinetic profile but without vasodilatory action and may be useful in controlling proximal hypertension. We compared its haemodynamic effects and neurological outcome with sodium nitroprusside during thoracic aortic cross clamp.

METHODS:

After institutional approval left thoracotomy was performed on 18 anaesthetised dogs and thoracic aorta was cross clamped for 30 minutes. The control group received no treatment of hypertension during cross clamp. In the other two groups proximal hypertension was controlled to 100mmHg using infusions of sodium nitroprusside (dosage range 2-10μg.kg.min^{-1}) or esmolol (dosage range 500-1000μg.kg.min^{-1}) respectively. Proximal and distal aortic pressures, central venous pressure, spinal cord perfusion pressure and cardiac output were monitored throughout. Neurological outcome was assessed twenty four hours after clamp release.

RESULTS:

In both groups control of hypertension was effective. Cardiac output fell significantly in the esmolol group compared to both other groups (Table 1). Despite this spinal cord perfusion pressure was best maintained in the esmolol group (Table 1) as distal arterial pressure was significantly higher ($p<0.05$) and cerebrospinal fluid pressure significantly lower ($p<0.05$) than in the sodium nitroprusside group.Three dogs died from surgical complications - one in the esmolol group and two in the control group. All surviving control animals were neurologically normal. Four of the five esmolol dogs were normal and the last paraplegic. All sodium nitroprusside dogs had neurological deficit ranging from paraplegia (n=5) to paraparesis (n=1).

DISCUSSION:

This study demonstrates that esmolol preserves spinal cord perfusion pressure when used to control proximal hypertension during thoracic aortic cross clamp. It may be a superior pharmacological agent to sodium nitroprusside in this situation. However its profound negative inotropic effect may preclude its use in patients with impaired left ventricular function.

TABLE 1

	Baseline	Cross Clamp at 30 mins	
Spinal Cord Perfusion Pressure (mmHg)			
Control	113± 4.3	18.6±3.6	
Esmolol	114±4.06	23.5±6.2	
Sodium Nitroprusside	105.5±9	5.3±4.5	A
Cardiac Output L/M			
Control	3.62 ±0.5	3.1±0.2	
Esmolol	3.57±0.5	0.64±0.1	B
Sodium Nitroprusside	3.72±0.6	4.5±0.7	

All values expressed as mean ± SEM

A p value <0.05 comparing sodium nitroprusside to both control and esmolol groups

B p value <0.05 comparing esmolol to both control and sodium groups.

S259

TITLE: OXYGEN IN CANINE HEART TISSUE DURING SIMPLE HYPOTHERMIC STORAGE

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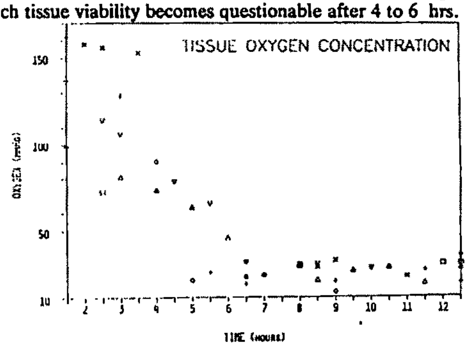
Current techniques for the preservation of donor myocardia for transplantation consists of cardioplegia, followed by placement into a hypothermic storage solution. Both laboratory and clinical experience suggests that this technique is only adequate for 4 to 6 hours, with tissue viability relating to the direct effects of cold as well as depletion of high energy phosphates. Anaerobic glycolosys results in the accumulation of metabolic products such as lactate, H^+, and inorganic phosphates, which cause a fall in intracellular pH, followed by the decline in ATP production. This study attempts to establish tissue partial pressure of oxygen following infusion of cardioplegic solution and to monitor the consumption dynamics of oxygen during simple hypothermic storage.

Six dogs were anesthetized and ventilated with 60% oxygen. Following a midline thoracotomy and dissection, cardioplegia, consisting of modified Collin's solution was instituted. After heart extraction, it was placed into the same cardiopleg solution. Temperature was maintained between 3 and 4°C in a specially designed insulated chest. Measurement of oxygen was achieved by insertion of a micro-dialysis probe into the middle layer of the anterior wall of the left ventricle. To prevent contamination from the storage solution, the probe was inserted so that the distance between the ends of the membrane and the insertion and exit points was approximately 15 mm. The dialysis probe was perfused at 5 ul/min with a modified Collin's solution equilibrated with nitrogen. Hypothermic storage was maintained for 12 hrs.

Initial O_2 tension in the dialysis probe outflow one hour after removal of the heart was slightly lower than in arterial blood sampled from the aortic arch just prior to cardioplegia. Without regard to the initial pO_2 in the blood, and the tissue immediately following cardiopleg infusion, the drop in pO_2 in the dialysis probe outflow in all experiments was similar, and completely disappeared after 4 to 5 hours.

Oxygen present in the heart tissue will diffuse into the dialysis perfusate along its concentration gradient. Under these conditions, the average concentration of oxygen from microvessels, extra and intracellular space should be observed. The volume of oxygen in the tissue and infused cardiopleg solution was expected to maintain full aerobic metabolism for no more than 20 to 30 minutes. The complete disappearance of tissue oxygen after 4 to 5 hours suggests that both aerobic and anaerobic metabolic mechanisms may be operational. Our results correlate well with clinical experience in which tissue viability becomes questionable after 4 to 6 hrs.



S260

TITLE: BILATERAL STELLATE GANGLIONECTOMY UNDER GENERAL ANESTHESIA REDUCES ATRIOVENTRICULAR CONDUCTION IN DOGS

AUTHORS: K. Sato, M.D., F. Murakami, M.D., T. Yamamura, M.D., O. Kemmotsu, Ph.D.
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Although thoracic epidural block or stellate ganglion block during anesthesia improve myocardial blood flow, the block may impair atrioventricular (AV) conduction. The present study was designed to examine effects of bilateral stallete ganglionectomy (BSG) under various volatile anesthetics on AV conduction in dogs.

Thirty two mongrel dogs were randomly divided into two groups:16 for group A (test) and 16 for group B (control). Anesthesia was induced with thiamylal and the trachea was intubated. Mechanical ventilation with 50% nitrogen and 50% oxygen was performed to keep normocapnia. Fentanyl 5ug/kg IV was supplemented. End-tidal anesthetic concentrations were continuously monitored with an infrared analyzer. After the control measurement of the cardiac electrophysiological variables (CEVs), BSG was performed in group A. Measurements of CEVs were repeated at 0, 0.5, 1.0 and 1.5 MAC of volatile anesthetics (sevoflurane, isoflurane, enflurane and halothane)in both groups.

After BSG, HR and arterial blood pressure (ABP) reached 80% of control values. In group B, HR and ABP remained unchanged throughout the course of the experiments. In group A, sinus cycle length (SCL) increased significantly at 0.5 MAC of all volatile anesthetics. Atrial-His length (AH) increased at 0.5 MAC isoflurane and at 1.5 MAC of other anesthetics (figure). Functional refractory period (FRP) of AV node increased at 0.5 MAC halothane and at 1.0 MAC of other anesthetics. In group B, SCL, AH and FRP were unchanged. His-ventricle interval and QRS-width remained unchanged throughout the experiments in both groups. We conclude that the intracardiac conduction is depressed by BSG during general anesthesia with volatile anesthetics.

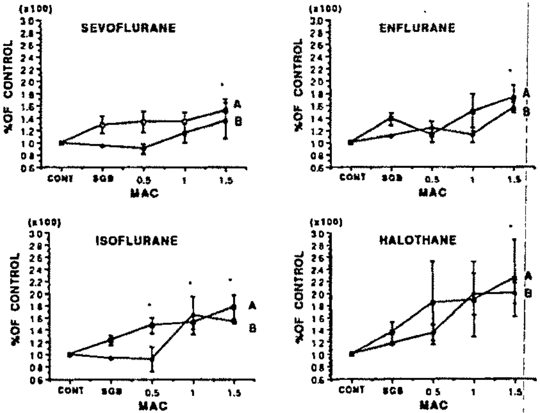

Figure: Effects of atrial-His interval (AH) in both groups. Bars indicate SEM. * P<0.05 vs control.

S261

TITLE: DEXMEDETOMIDINE INHIBITS SYNAPTIC TRANSMISSION IN THE CANINE STELLATE GANGLION

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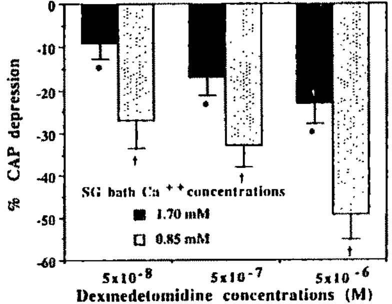
The inhibitory effects of α_2-adrenoceptor agonists (AAA) on central sympathetic outflow at the spinal and cranial CNS level have been well established[1]. However, AAA effects on the peripheral sympathetic nervous system (SNS) remain to be elucidated. Therefore, we examined the effect of dexmedetomidine (DMT), a selective AAA, on synaptic transmission in the canine stellate ganglion (SG) in vitro.

14 SG were isolated from adult mongrel dogs after halothane anesthesia, desheathed and superfused with Krebs' solution equilibrated with 97% O_2-3% CO_2 mixture and maintained at 37 °C and pH 7.4. The preganglionic T_3-ramus and postganglionic ventral ansa subclaviae were placed on bipolar tungsten electrodes for stimulating and recording purposes, respectively. Ganglionic transmission was measured by recording the compound action potential (CAP) under conditions of supramaximal electrical stimulation at 0.4 Hz. Evoked CAP were displayed on a digital oscilloscope and recorded/processed with the help of an analog output MacADIOS-IISE Superscope (GW Instruments) interfaced with an Apple Macintosh-SE computer. The percent CAP change from control was measured following SG superfusion with log step increments of DMT 5.5×10^{-9} to 10^{-6}M and equimolar concentrations of the AA-antagonist yohimbine (Y), respectively. DMT and Y were administered in alternating order for 15-min periods of exposure at each log concentration. Hexamethonium (5×10^{-5}M) was used at the end of each experiment to verify the synaptic nature of the CAP.

DMT caused a dose-dependent CAP depression (fig) which was specifically and consistently reversed by Y. To examine whether this effect involved the mediation of calcium (Ca^{++}), we used bath Ca^{++} concentrations of 0.85 mM in one group (n=8) and 1.7 mM in the other group of experiments (n=6). Part of the DMT-induced CAP depression was overcome by increasing extracellular Ca^{++} concentrations (fig) suggesting that AAA may modulate Ca-mediated neurotransmitter release presynaptically. We conclude that AAA have potent inhibitory effects on the peripheral SNS in addition to their well known central inhibitory actions. These effects may be Ca-mediated. Peripheral AAA may have important physiological and potential therapeutic implications for the control mechanisms that regulate cardiopulmonary functions.

Dexmedetomidine induced inhibition
of synaptic transmission in the canine stellate ganglion (SG)



*p <0.01 vs. 0 DMT; †p <0.05 vs. 1.7mM Ca++

Reference: 1)Anesthesiology 74:581-605, 1991

S262

Title: HEMODILUTION DURING CEREBRAL ISCHEMIA IN RATS: EFFECTS OF STROMA-FREE HEMOGLOBIN ON BLOOD FLOW

Authors: RM Schell MD, DJ Cole MD,
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Introduction: During surgical procedures at risk for cerebral ischemia, hemodilution has been proposed to ameliorate brain injury. However, the efficacy of hemodilution therapy is limited by an accompanying decrease in oxygen content.[1] We assessed the effect of hemodilution, with stroma-free hemoglobin (SHgb, 7 g·dl^{-1}), on cerebral blood flow (CBF) after middle cerebral artery occlusion (MCAo) in rats.

Methods: Following approval by the Animal Care Committee, rats were anesthetized with 1.2 MAC isoflurane. Each animal was given SHgb (viscosity≈1.3) to achieve one of the following hematocrits (Hct):

Control (n=8)-Hct 44%	23/Hct (n=8)-Hct 23%
37/Hct (n=8)-Hct 37%	16/Hct (n=8)-Hct 16%
30/Hct (n=8)-Hct 30%	9/Hct (n=8)-Hct 9%

Donor blood (viscosity≈4.0) was given to maintain an equal blood volume between groups. After 10-min of MCAo, CBF was assessed with ^{14}C-iodoantipyrine.[2] A coronal brain section in the ischemic zone was assessed to define areas with a CBF of 0-10 and 11-20 ml·$100g^{-1}$·min^{-1}. The data were compared by analysis of variance and multiple linear regression analysis.

Results: Both CBF areas were less in the 30/Hct, 23/Hct, and 16/Hct groups vs the Control and 37/Hct groups ($p<0.05$, see Table 1). In addition, both CBF areas were less in the 9/Hct group vs the other five groups ($p<0.05$).

Discussion: The results of this study support a hypothesis that hemodilution with SHgb decreases the extent of focal cerebral ischemia. Further studies are indicated to assess if this decrease in ischemia correlates with brain injury.

Group	0-10 CBF	11-20 CBF
Control	19.9±3.5	22.2±3.1
37/Hct	21.2±3.2	22.9±4.6
30/Hct	14.1±3.0*	14.9±4.4*
23/Hct	13.2±3.9*	13.2±2.3*
16/Hct	12.3±3.0*	12.9±4.1*
9/Hct	7.6±3.8†	8.3±2.8†

Table 1-% of hemisphere ipsilateral to MCAo with a CBF of 0-10 and 11-20 ml·$100g^{-1}$·min^{-1} (mean±SD). *$p<0.05$ vs the Control and 37/Hct groups. †$p<0.05$ vs the other five groups.

References:
1. *Stroke* 20:423-427, 1989.
2. *Anesthesiology* 71:580-585, 1989.

S263

TITLE: Hemodynamic and Catecholamine Responses Following Endotracheal Intubation Using Succinylcholine Versus Vecuronium

AUTHORS: H Schieren PhD, M Heropoulos MD, J Seltzer MD, R Bartkowski MD, PhD, J Lessin RN, M Torjman MEd, C Moody BA, M Goldberg MD
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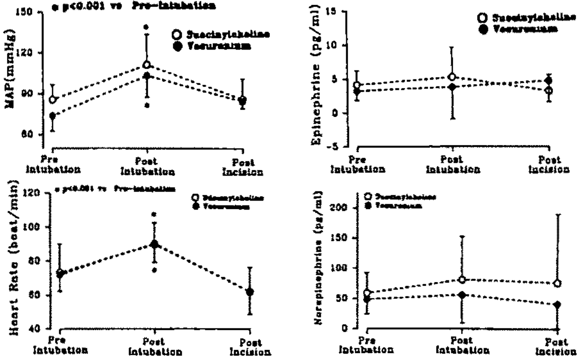
Introduction: Plasma norepinephrine levels and arterial pressure have been shown to increase following intubation(1). Interestinly, succinylcholine (SUC) administration has itself been shown to raise the plasma concentration of norepinephrine(2). Under most clinical conditions, this SUC-induced elevation in circulating catecholamines should coincide with the sympathetic stimulation from intubation. Therefore, we compared the hemodynamic stability and catecholamine activity post intubation using SUC with that using vecuronium (VEC).

Methods: After IRB approval and informed consent, we studied 20 ASA I-III patients, ages 18-75, scheduled to undergo limb surgery. Patients were premedicated with diazepam (5mg orally), and received tubocurarine (3mg I.V.) to prevent fasiculation. Induction agents included: thiopental (4mg/kg and 50mg increments as required); fentanyl (2μg/kg); and either VEC (0.1mg/kg) or SUC (1.5mg/kg), according to a randomized assignment code. Mean arterial pressure and heart rate were recorded by an automated blood pressure cuff. Plasma catecholamines were measured by HPLC with ECD.

Statistical analyses were performed by ANOVA with repeated measures, using the LSD test for the comparison of individual means; $P < 0.05$ was considered to be statistically significant.

Results: Hemodynamic parameters were not significantly different between SUC and VEC groups, although both the mean arterial pressure ($p < 0.001$) and heart rate ($p < 0.001$) increased significantly within each of these groups at post-intubation. Norepinephrine and epinephrine levels did not differ significantly between, or within, SUC and VEC groups.

Discussion: Both SUC and VEC groups evidenced a significant elevation in mean arterial pressure and heart rate following intubation. SUC, however, did not appear to precipitate a greater hemodynamic response to intubation than did VEC. In addition, the catecholamine and hemodynamic responses to intubation were apparently not coupled in these patients. It may be that fentanyl(3) and tubocurarine(4) alter hemodynamic/ hormonal responses to intubation, even at the low dosages employed in this study. Alternatively, it is possible that hypertensive pathway(s), other than the sympathoadrenal circuit, contribute to the intubation response(5).



1. Br.J.Anaesth. 53:837-839. 1981
2. Anesth. Analg. 62:627-632. 1983
3. Anesthesiology 73: 5-11. 1990
4. Anesth. Analg. 72:84-88. 1991
5. Anesth. Analg. 72: S236. 1991

S264

TITLE: DEXMEDETOMIDINE ATTENUATES THE "SHIVERING" UPON EMERGENCE FROM HALOTHANE ANESTHESIA IN CHRONICALLY INSTRUMENTED CATS

AUTHORS: WT Schmeling MD PhD, JP Kampine MD PhD, DC Warltier, MD PhD
AFFILIATION: Depts. of Anesthesiology & Pharmacology, Medical College of Wisconsin, Milwaukee, WI 53226

Emergence from anesthesia with the volatile agents, including halothane (HAL), is often complicated by hemodynamic instability and an activation of electromyographic (EMG) activity grossly resembling shivering[1]. The alpha$_2$ adrenergic agonist, dexmedetomidine (DEX), has been previously demonstrated to attenuate the hemodynamic responses after enflurane anesthesia[2] and to decrease spontaneous EMG activity[3]. The purpose of the present investigation was to examine the actions of DEX on EMG "shivering" after HAL anesthesia.

With prior Animal Care Committee approval, anesthetized cats (N=6) were instrumented for measurement of the electroencephalogram, the fore- and hind-limb EMG, hypothalamic (HYP) temperature (T°), core T°, paw and upper limb skin T°, to calculate the T° gradient, as an index of thermoregulatory vasoconstriction[1]. Thermodes were also placed in the HYP to selectively heat or cool the HYP and induce thermoregulatory responses. Animals were allowed to recover from surgery 7-14 days prior to experimentation. After obtaining conscious control responses, animals were anesthetized with HAL (1.5 to 2.0%, end tidal) for 0.5-1.0 hours. HAL was discontinued and emergence EMG responses quantitated. During active EMG "shivering" activity, DEX (2.5-5.0 μg/kg i.v.) was administered and EMG and T° changes quantitated. All integrated EMG data were expressed as % conscious control activity. Statistical analysis changes between conscious control and anesthetic interventions were compared by ANOVA with repeated measures followed by Bonferroni's t-test (*$p<0.05$).

Heating or cooling of the HYP during conscious control conditions resulted in EMG shivering and T° gradient changes consistent with normal thermoregulatory responses, which were absent during normothermic HAL anesthesia. Emergence from HAL was characterized by significant EMG activation (increased to 804±46% of conscious control) and restoration of an appropriate T° gradient. Administration of DEX dose-dependently significantly decreased (71±15 and 96±5% of conscious control, at 2.5 and 5.0 μg/kg, respectively) the emergence EMG "shivering" activity. DEX also induced mild hypothermia but T° gradients and thermoregulatory response to HYP thermal challenge remained intact. These results indicate that DEX abolishes the increase in EMG activity after HAL anesthesia and these effects might provide a useful adjunct for general anesthesia.

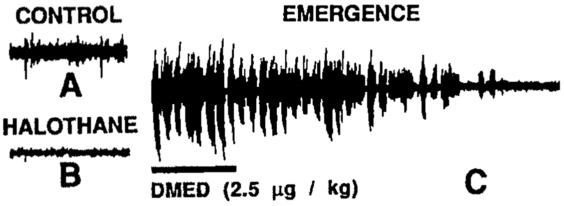


Figure EMG during conscious control (A), HAL (B) and emergence with administration of DEX (C).

References:
1) *Anesthesiology* 68:833, 1988; 2) *Anesthesiology* 74:108, 1991; 3) *The Pharmacologist* 32:129, 1990.

S265

TITLE: THE QUALITY OF SHED MEDIASTINAL BLOOD COMPARED TO BANKED BLOOD

AUTHORS: H. Schmidt, M.D.[1], U. Kongsgaard, M.D.[2], F. Brosstad, M.D.[1], J. Kofstad, M.D.[1], O. Geiran, M.D.[1].
AFFILIATION: Depts. of Anaesthesia, Medicine, Clinical Chemistry, and Surgery. [1]The National Hospital and [2]The Norwegian Radium Hospital, Oslo, Norway.

INTRODUCTION: Autotransfusion of shed mediastinal blood after open heart surgery has been reported to be a safe procedure. An important question is, however: what is the quality of the red blood cells in the reinfused shed blood compared to the alternative; banked blood?

METHODS: 10 patients undergoing open heart surgery received postoperative autotransfusion of shed mediastinal blood collected in the cardiotomy reservoir. Patient blood and shed blood from the reservoir as well as banked blood (3 weeks old and 5 weeks old SAGMAN blood) were investigated. Haemoglobin concentration and oxygen saturation were measured using a multi-wavelength hemoximeter. pH, pCO_2, and pO_2 were measured using a blood gas analyzer. The concentration of extractable oxygen (c_x) and half saturation tension (p50) were calculated using the Oxygen Status Algorithm as described elsewhere (1). Osmotic resistance of the red blood cells was measured using a gradient series of increasing saline solutions.

RESULTS: Mean haemoglobin concentration was 88 g/l in shed blood and 212 g/l in banked blood. Mean pH in shed blood was 7.45 while 6.38 in banked blood. Concentration of extractable oxygen of the shed blood was lower (not significantly) than in patient blood but significantly higher than in banked blood. The p50 was in normal range for all blood tested, but lower in banked blood. Osmotic resistance of the erythrocytes in shed blood was normal, while decreased in the banked blood cells (more in 5 weeks old than in 3 weeks old).

Discussion: Previous studies have shown that shed mediastinal blood has undergone coagulation and fibrinolysis (2). Some destruction of red cells also takes place. The results from this study show that the quality of the remaining erythrocytes in the shed blood is acceptable and superior compared to banked blood.

References:
1) Scand J Clin Lab Invest 1990:50, Suppl. 203:29-45.
2) Acta Anaesthesiol Scand 1991:35:71-76.

S266

Title: DO PATIENTS REALLY WANT TO KNOW THEIR HIV STATUS?

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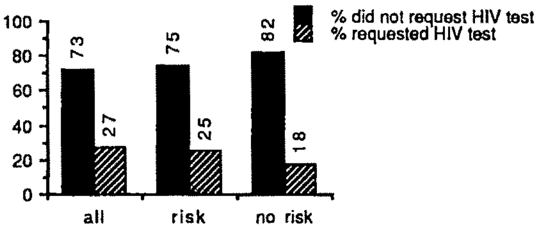
Introduction: There is a current perception among legislators that the public is moving toward universal HIV testing in order to control the spread of the HIV virus. We wished to determine if this perception held true for our patient population. Using a portable, automated device (HealthQuiz), an extensive medical history was obtained from patients to test the hypothesis that people would choose to learn their own HIV status.

Methods: After IRB approval, 226 randomly chosen ambulatory surgery patients in a preoperative clinic completed the HealthQuiz. Patients answered up to 130 questions about their general health. From among those questions, four "HIV risk indicator" questions asked whether patients had had blood transfusions since 1979, whether patients had used IV drugs, whether patients had been exposed to the body fluids of anyone likely to have HIV, and whether patients considered themselves to be in a high-risk category for HIV. All patients then were asked whether they would like to receive a test to find out if they had been exposed to the AIDS virus.

Results: Of 226 patients, 61 (27%) requested an HIV test and 165 (73%) did not request an HIV test. If a patient answered positively to at least one of the four "risk identifier" questions, then the patient was assigned to the "declared risk group." All other patients were assigned to the "no declared risk group." Of the 226 patients, 53 (23%) put themselves into the declared risk group while 173 patients (77%) put themselves into the no declared risk group. In the no declared risk group, 82% did not wish to learn HIV status. More importantly, in the declared risk category, 75% did not wish to learn their HIV status even though they had admitted to at least one risk indicator.



Discussion: State and federal legislators currently hold that the public demands protection from the HIV virus via HIV testing. This belief is used to garner support for laws to implement the mandatory HIV testing of healthcare workers. However, our study demonstrates that the majority of our patients, regardless of their declared risk group status, were unwilling to request HIV testing for themselves. Legislators may benefit from studies such as this one before using their perception of the public will to justify mandatory HIV testing laws.

S267

Title: CEREBRAL BLOOD FLOW DURING LOW-FLOW HYPOTHERMIC CARDIOPULMONARY BYPASS IN BABOONS
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Introduction: A time-dependent decline in cerebral blood flow (CBF) has been reported to occur during full-flow (2L/min/m^2) cardiopulmonary bypass(CPB).[1] This was measured despite constant CPB flow, Hct, temp, systemic blood pressure and pCO$_2$.[2] Low-flow CPB (0.5L/min/m^2) has gained popularity for complex cardiothoracic surgical procedures. With flows at 25% of full-flow bypass a time-dependent decline in CBF could magnify the risk of neurologic injury.

Methods: Six baboons received im ketamine (10mg/kg). After tracheal intubation, ventilation was controlled and anesthesia maintained with fentanyl 10μg/kg followed by 2μg/kg/hr iv, midazolam .03mg/kg/hr and isoflurane (0.25% end-tidal concentration) in O$_2$. Femoral arterial and venous catheters were inserted. EKG, blood pressure, tympanic and rectal temp., end-tidal CO$_2$ and isoflurane concentration were continuously recorded. Vecuronium was used for neuromuscular blockade. After sternotomy, a 24-gauge catheter was inserted into the common carotid artery and the ipsilateral external carotid temporarily occluded. Aortic and vena caval cannulae were inserted and CPB initiated. Baboons were cooled at a flow of 2.5L/min/m^2 until tympanic membrane temp. decreased to 18°C. CPB flow was then reduced to 0.5L/min/m^2 and maintained constant for at least 70 min. Thereafter CPB flow was increased to 2.5L/min/m^2 and baboons rewarmed to normal temp. CPB was terminated after return of cardiac function. CBF was measured before CPB, during full-flow CPB, during stable low-flow CPB at 30-min intervals, during full-flow CPB before rewarming and after termination of CPB. For each determination, 700μCi of ^{133}Xe in 0.8ml saline was injected into the common carotid and flushed with 2ml of saline. Single collimators detected radioactive washout with a Novo Cerebrograph 10a and CBF was determined by the initial slope corrected for Hct and temp.[3] CBF values were compared by repeated measures ANOVA. $P < 0.05$ was significant.

Results: Values for CBF are shown in the Table. CBF declined 50-60% from pre-bypass values during low-flow CPB. CBF did not change with time during stable (unchanged temp, pCO$_2$, BP) low-flow CPB.

Discussion: In contrast to full-flow CPB, low-flow CPB does not cause a time-dependent decline in CBF. Previous suggestions that CPB is associated with either progressive cerebral vasoconstriction or microvascular obstruction from accumulating debris do not apply to the low-flow state. The continued high incidence of transient and permanent neurologic complications from CPB can not be explained by progressive time-dependent changes in CBF during low-flow hypothermic bypass.

References: 1) *Anesthesiology* 1988;69:547
2) *Anesth Analg* 1991;72:161
3) *Anesthesiology* 1990;73:637

CEREBRAL BLOOD FLOW (ml/min/100g)
n = 6; mean (SD)

Pre-bypass	*Full Flow*	*Low Flow*	*Low Flow*	*Low Flow*	*Full Flow*	*Post-bypass*
25.1	37.0	12.6*	11.1*	13.2*	35.4	36.8
(4.3)	(18.1)	(4.8)	(3.3)	(4.6)	(28.5)	(23.4)

***$P < 0.05$ compared to pre-bypass, full flow or post-bypass**

S268

TITLE: POSTOPERATIVE COMPLICATIONS FOLLOWING SPINAL FUSION IN CHILDREN - IS INTENSIVE CARE ALWAYS NECESSARY?

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Spinal fusion (SF) for scoliosis is a major surgical procedure with the potential for large blood loss. Pediatric scoliosis occurs during adolescence (idiopathic scoliosis - IS) or secondary to neuromuscular disease (ND). At our institution, all children are admitted to an ICU following SF. This retrospective review was done to document complications in the postoperative period for children with IS and ND.

The charts of 106 children undergoing posterior SF during 1989 were reviewed (19 not available). Not included were patients >19 yrs. and those with anterior fusions. Hemodynamic data, vital signs and laboratory values in the PACU and ICU were recorded. Results appear in Tables I-III.

Frequent complications in the PACU included acidosis (pH$<$7.3) 57%, oliguria ($<$1cc/ kg/ hr) 55%, anemia (HCT$<$30) 43% and hypothermia (T$<$35) 30%. In the ICU, fever (T$>$38), anemia, oliguria and coagulopathies were noted in $>$70% of all patients. Serious complications (Vent assistance, Hypoxemia, Pressor Support) occurred in some ND patients, but less often or not at all in healthy IS patients. The only cardiac arrest was in the ND group.

It appears from these data that following SF, some complications were very frequent in all patients. Serious complications, however, occurred primarily in the ND group. An ICU may not be necessary for some healthy children with IS following spinal surgery.

TABLE 1

	#	AGE (YR)	SEX	OR TIME (HRS)	EBL (MLS)	DAYS IN ICU
IS	60	14.5	M13 F47	5.2	1489	1.2
ND	46	12.4	M14 F32	5.5	1787	1.4
TOTAL MEAN	106	13.6	M27 F79	5.3	1619	1.3

TABLE II

PACU COMPLICATIONS (#PTS)

	ACIDOSIS	↓TEMP	↓U/O	↓HCT
IS	31	19	35	21
ND	26	12	21	21
TOTAL (%)	57	30	55	43

TABLE III

ICU COMPLICATIONS (#PTS)

	VENT ASST.	↓PO$_2$	↑TEMP	↓HCT	ABNL COAGS	ABNL LYTES	↓BP	↓U/O
IS	1*	4*	54	44	40	1	1*	57
ND	3	10	39	31	26	4	2	38
TOTAL (%)	4	14	88	71	71	5	3	92

*INCLUDES ONE CHILD WITH CYNOTIC CHD

S269

EXPLICIT AND IMPLICIT MEMORY AND MID-LATENCY AUDITORY EVOKED POTENTIALS DURING CARDIAC SURGERY

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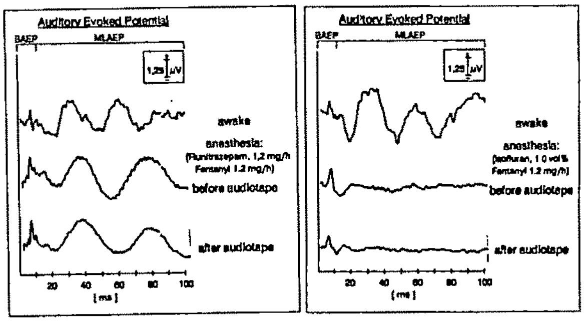
There is a high incidence of intraoperative awareness during cardiac surgery. In the present study, we investigated mid-latency auditory evoked potentials (MLAEP) and explicit and implicit memory for information presented during cardiac anesthesia.

Institutional approval and informed consent was obtained in 45 patients scheduled for elective cardiac surgery. Anesthesia was induced in group I (n=10) with Flunitrazepam/ Fentanyl (0.01 mg/kg) and maintained with Flunitrazepam/ Fentanyl (1.2 mg/h). The patients of group II (n=10) and III (n=10) received Etomidate (0.25 mg/kg) for induction and Isoflurane (0.6-1.2 vol%)/ Fentanyl (1.2 mg/h) or Propofol (4-8 mg/kg/h)/ Fentanyl (1.2 mg/h) for maintenance of general anaesthesia. Group IV (n=15) served as a control and patients were anesthetized as in I, II or III. After sternotomy an audiotape was presented to the patients of group I, II and III, which included an implicit memory task. The story of *Robinson Crusoe* was told and the patients were suggested to remember *Robinson Crusoe* when they were asked to their associations to *Friday* 3-5 days postoperativly. Auditory evoked potentials were recorded awake and during general anesthesia before and after the audiotape presentation on vertex (positive) and mastoides on both sides (negative). Auditory clicks were presented binaurally at 70 dBnHL with a frequency of 9.3 Hz. Using the electrodiagnostic system Pathfinder I (Nicolet), 1000 successive stimuli were averaged over a 100 ms poststimulus period and analysed off-line. Latencies of the peak V, Na, Pa were measured. V belongs to the brainstem generated potentials, which demonstrates that auditory stimuli were correctly transduced. Na, Pa are generated in the primary auditory cortex of the temporal lobe and are the elektrophysiological correlate of the primary cortical processing of the auditory stimuli.

No patient had an explicit memory for intraoperative events. 5 patients in group I, 1 patient in group II and III, no patient in group IV showed implicit memory for the intraoperative tape message. They remembered *Robinson Crusoe* spontanously when they were asked to their associations to *Friday*. In the awake state AEP peak latencies were in the normal range. During general anaesthesia in group I, latencies of the peaks Na, Pa did not increase in latency or decrease in amplitude before and after the audiotape presentation. The primary cortical complex Na/Pa could be identified like in the awake state. In contrast in group II and III Na, Pa showed a marked increase in latency and decrease in amplitude or were completly suppressed (see fig.).

During general anesthesia auditory information can be processed and remembered postoperatively by an implicit memory function, when the electrophysiological conditions of primary cortical stimuli processing is preserved. Implicit memory can be observed more often when high dose Opioid analgesia is combined with receptor-binding agents like Benzodiazepines, than under non-specific anesthetics like Isoflurane or Propofol. Non-specific anesthetics seem to provide a more effective suppression of auditory stimuli processsing than receptor specific agents.



S270

EFFECTS OF THIOPENTONE ON MID-LATENCY AUDITORY EVOKED POTENTIALS

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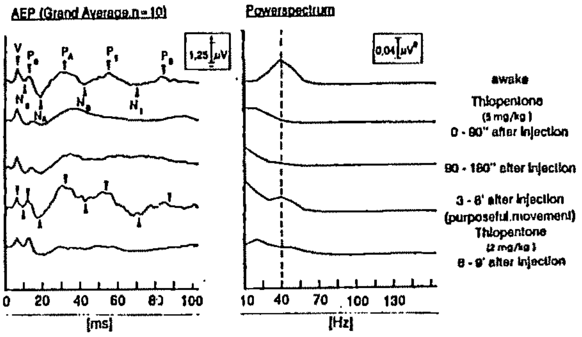
Thiopentone is the anesthetic most often used for induction of general anesthesia. The effects of Thiopentone on mid-latency auditory evoked potentials (MLAEP) has not yet been studied. Therefore, MLAEP during induction of general anesthesia with Thiopentone were studied.

Institutional approval and informed consent was obtained in 10 patients scheduled for minor gynaecological procedures. Anesthesia was induced with Thiopentone (5 mg/kg). Assisted ventilation via face mask with 100% O_2 was performed until the first purposeful movement of the limbs appeared. Then a second bolus of Thiopentone (2 mg/kg) was given and general anaesthesia was maintained according to anesthesiological and operative necessities. Auditory evoked potentials were recorded before and on-line when Thiopentone was injected up to 9' after the onset of general anaesthesia on vertex (positive) and mastoides on both sides (negative). Auditory clicks were presented binaurally at 70 dBnHL with a frequency of 9.3 Hz. Using the electrodiagnostic system Pathfinder I (Nicolet), 1000 successive stimuli were averaged over a 100 ms poststimulus period and analysed off-line. Latencies of the peak V, Na, Pa, Nb, P_1, N_1 were measured. V belongs to the brainstem generated potentials, which demonstrates that auditory stimuli were correctly transduced. Na, Pa, Nb, P_1, N_1 are generated in the primary auditory cortex of the temporal lobe and are the electrophysiological correlate of the primary cortical processing of the auditory stimuli. A Fast Fourier transformation calculated powerspectra of the AEP.

In the awake state AEP peak latencies were in the normal range. Powerspectra indicated high energy in the 30-40 Hz frequency range. After induction of general anaesthesia latencies of the peaks Na, Pa, Nb, P_1, N_1 increased or were even completely suppressed. In the power spectra 40 Hz energy became suppressed too. These effects were observable until 3 min after injection. When the first purposeful movement of a limb occurred MLAEP latencies returned to normal values and high energy could be found in the 30-40 Hz range as in the awake. A second bolus of Thiopentone again led to an increase in MLAEP latencies and a suppression of the energy in the 30-40 Hz range (see fig.).

Anesthetic effects of Thiopentone can be monitored by MLAEP recording. Clinical signs of decreasing anesthetic action (spontaneous movements) coincide with the reversibility of MLAEP changes under Thiopentone.



S271

ENFLURANE AND ISOFLURANE CAUSE A DOSE DEPENDENT DECREASE OF NEURONAL OSCILLATIONS IN AUDITORY EVOKED POTENTIALS

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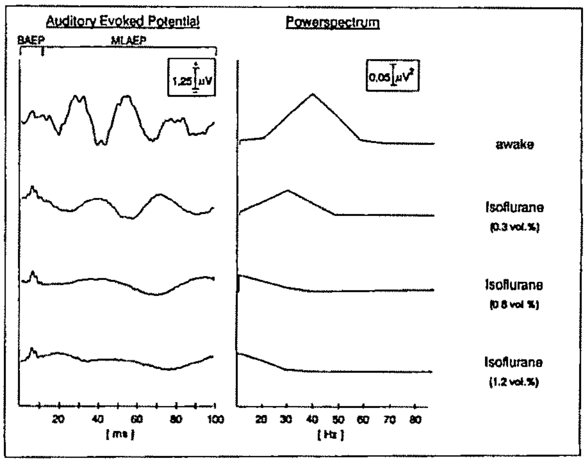
Neuropsychological and neurophysiological investigations indicate that a 30-40 Hz oscillatory brain mechanism is necessary for the adequate uptake and processing of elementary successive sensory events. An oscillatory component of that particular frequency range can be observed in the mid-latency auditory evoked potentials (MLAEP). General anesthesia may be defined as a suppression of sensory information processing. We studied the dose-dependent effects of Isoflurane (I) and Enflurane (E) on MLAEP and the auditory evoked neuronal 30-40 Hz oscillation.

Institutional approval and informed consent was obtained in 24 patients scheduled for elective laparotomy. Continuous epidural analgesia was performed to block the painful sensation of surgical stimuli. MLAEP were recorded in the awake state and during general anesthesia with I (group I, n=13) after 15' steady state endexspiratory concentration 1.2, 0.6, 0.3 vol% or E (group II, n=11) 1.6, 0.8, 0.4 vol%. MLAEP were recorded on vertex (positive) and mastoides on both sides (negative). Auditory clicks were presented binaurally at 70 dBnHL with a frequency of 9.3 Hz. Using the electrodiagnostic system Pathfinder I (Nicolet), 1000 successive stimuli were averaged over a 100 ms poststimulus period and analysed off-line. Latencies of the peak V, Na, Pa, Nb, P_1, N_1 were measured. V belongs to the brainstem generated potentials, which demonstrates that auditory stimuli were correctly transduced. Na, Pa, Nb, P_1, N_1 are generated in the primary auditory cortex of the temporal lobe and are the electrophysiological correlate of the primary cortical processing of the auditory stimuli. A Fast-Fourier transformation calculated powerspectra of the AEP.

In the awake patients MLAEP had an oscillatory wave form. Powerspectra indicated the major energy in the 30-40 Hz frequency range. Under general anesthesia with I or E there was a statistically significant dose-dependent linear increase in peak latencies Na, Pa, Nb, P_1, N_1 and decrease in amplitude Na/Pa. The oscillation frequency decreased first to 30 Hz under subanesthetic concentrations (¼ MAC) and to 10-20 Hz under anesthetic concentrations (½-1 MAC) (see fig.). The energy in the 30-40 Hz frequency range became progressively suppressed with increasing concentrations of the volatile anesthetics I or E.

These results support the concept that the underlying framework of sensory information processing is a stimulus-dependent, oscillatory brain mechanism. General anesthesia with Isoflurane and Enflurane suppresses these oscillations in MLAEP dose-dependently. MLAEP-monitoring could be a useful tool to monitor central anesthetic actions.



S272

POSTANESTHETIC COGNITIVE AND PSYCHOMOTORIC IMPAIRMENT AFTER INDUCTION AND MAINTENANCE OF ANESTHESIA WITH PROPOFOL. A COMPARISON WITH THIOPENTONE/ ISOFLURANE

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Institutional approval and informed consent was obtained in 40 female ASA I or II patients undergoing diagnostic laparoscopy. They were randomly assigned to receive either Propofol for induction and maintenance of anesthesia, or Thiopentone/ Isoflurane as part of a standard anesthetic technique including Alfentanil and Vecuronium supplemented by 50% nitrous in oxygen and a premedication with Bipotassium-chlorazepat.

Choice reaction time (CRT), the score in the Zahlen-Verbindungs-Test (ZVT) in which the patients had to connect numbers from one to ninety in subsequent order, Digit Span (DS), and the Münchner Gedächtnis Test (MGT), the german version of the California Verbal Learning Test were performed at four measurement points (mp): the day before the operation (mp 1) and 30' (mp 2), 60' (mp 3), and 240' (mp 4) after recovery. ZVT, DS and MGT were presented in four parallel forms to minimize learning effects. The State-Trate-Anxiety Inventory (STAI) was given at mp 1 and mp 4. The Wisconsin Card Sorting Test (WCST) was performed at mp 4.

The groups were comparable in age, weight, height and level of education. No significant difference was found in anesthesia time ($p=.916$) but recovery time (indicator was correct recall of birth date) was significantly ($p<.000$) shorter with Propofol.

Within subject analysis of means by Wilcoxon Matched-pairs Signed-ranks test showed significantly ($p<.01$) worse results in CRT and ZVT at every postoperative measurement point with the exception of mp4 in CRT only in the Propofol group and in ZVT for both groups. No significant differences were found for DS in both groups. For MGT a difference was found only between mp1 and mp 2 for both groups. Between subjects analysis of means by Man-Whitney U Rank Sum Test showed significantly ($p<.01$) better results in CRT and MGT at mp 3 and mp 4 for the Propofol group. Although the trend was the same for ZVT no significant result was detected. Also no significant difference was found for DS and WCST at all measurement points. The postoperative state anxiety was significantly ($p<.02$) lower in the Propofol group.

The result of this study concerning recovery time and CRT are congruent with reports from many other authors. Moreover, Propofol seems to produce less postoperative impairment in verbal memorization. DS and ZVT might not be sensitive enough to detect differences between the two anesthetic procedures for the capabilties measured. A widespread hypothesis that patients after anesthesia with Propofol seem to be in a better mood state is supported by the results in the STAI.

S273

INCREASING DOSAGES OF FENTANYL AND MID-LATENCY AUDITORY EVOKED POTENTIALS

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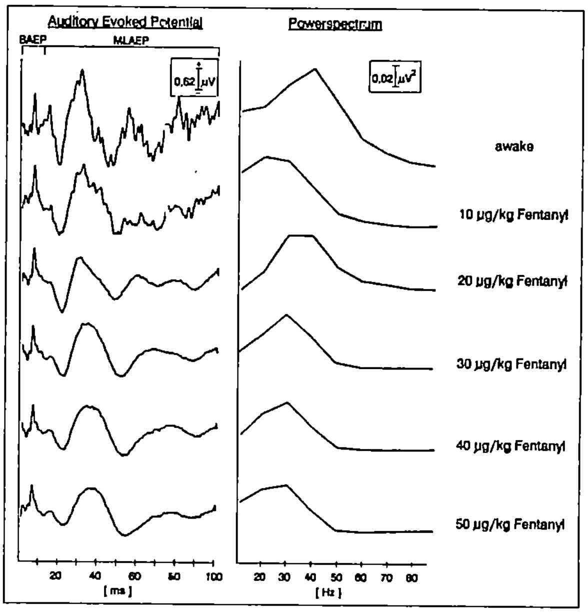
Opioids produce analgesia, sedation, and are also used for induction and maintenance of general anesthesia. Dose-dependent effects of Opioids on mid-latency auditory evoked potentials (MLAEP) have not yet been studied. Intraoperative awareness, and especially the perception of auditory stimuli are occasionally observed under general anesthesia with high-dose Opioids. We studied dose-dependent effects of Fentanyl on MLAEP.

Institutional approval and informed consent was obtained in 20 patients scheduled for cardiac surgery. Anesthesia was induced with Fentanyl (10 µg/kg every 5' up to a total dosage of 50 µg/kg). Auditory evoked potentials were recorded before and 5' after every Fentanyl dose on vertex (positive) and mastoides on both sides (negative). Auditory clicks were presented binaurally at 70 dBnHL with a frequency of 9.3 Hz. Using the electrodiagnostic system Pathfinder I (Nicolet), 1000 successive stimuli were averaged over a 100 ms poststimulus period and analysed off-line. Latencies of the peak V, Na, Pa, Nb, P_1, N_1 were measured. V belongs to the brainstem generated potentials, which demonstrates that auditory stimuli were correctly transduced. Na, Pa, Nb, P_1, N_1 are generated in the primary auditory cortex of the temporal lobe and are the electrophysiological correlate of the primary cortical processing of the auditory stimuli. A Fast-Fourier transformation calculated powerspectra of the AEP (see fig.).

In the awake state AEP peak latencies were in the normal range. Powerspectra indicated high energy in the 30-40 Hz frequency range. During increasing dosages of Fentanyl the brainstem response V was stable. There was only a small increase in latency and decrease in amplitude of P_1 and N_1. Whereas the primary cortical complex Na, Pa did not change even under highest doses of Fentanyl (50 µg/kg) and could be identified like in the awake patients. In the power spectra high energy persisted in the 30 Hz frequency range.

MLAEP and especially the primary cortical complex Na/ Pa do not change markedly in amplitude or latency during high-dose Fentanyl analgesia. There is no dose-dependent effect of opioids on MLAEP, and primary cortical processing of auditory stimuli seems to be preserved. This must be seen in connection with cases of awareness and perception of auditory stimuli during high-dose Opioid analgesia.



S274

Title: EFFECTS OF TRENDELENBURG POSITION ON SERUM CATECHOLAMINES AND HEMODYNAMICS IN AWAKE AND ANESTHETIZED PATIENTS

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INTRODUCTION: The head-down or Trendelenburg position was first described in the 1860's. It has subsequently been shown to affect hemodynamics and respiration. These changes, which represent a physiologic "stress," may influence the level of circulating catecholamines. We have evaluated the effects of changing from supine to Trendelenburg position (30 degree tilt) on the serum levels of epinephrine, norepinephrine, dopamine and hemodynamic changes in awake and anesthetized patients. Measured indices include mean arterial blood pressure (MBP), heart rate (HR), pulmonary artery diastolic pressure (PAD), central venous pressure (CVP) and cardiac output (CO).

METHODS: Institutional approval for the study and informed consents were obtained. We evaluated 12 patients prior to cardiac bypass surgery. Patients requiring hemodynamic support (pharmacological or mechanical) were excluded from the study. Swan-Ganz catheters and arterial cannulas were instituted in all patients after morphine (0.1 mg/kg) IM, diazepam 10 mg PO and scopolamine 0.3 mg IM premedication was administered. Hemodynamic measurements were made in the supine and Trendelenburg positions, allowing a 10 minute equilibration period after changing position. Following a cardiac anesthetic induction (sufentanyl 10-15 mcg/kg IV, midazolam and vecuronium 10 mg) and a 10 minute equilibration period, supine position anesthetized measurements were taken and serum catecholamine levels drawn from the arterial line. Variation between means were determined by the t-test, $p \leq 0.05$ was considered significant.

RESULTS: Serum epinephrine, norepinephrine and dopamine levels (evaluated in 10 patients) did not change significantly with respect to changing position in either the awake or anesthetized state. The serum epinephrine levels decreased from 99.8 ± 20.1 ng/l (SEM) awake to 33.9 ± 8.6 ng/l (SEM) after induction of anesthesia in the supine position ($p < 0.02$) and from 124.8 ± 29.4 ng/l to 39.1 ± 18.1 ng/l in the Trendelenburg position ($p < 0.01$). MBP was 98 mmHg ± 5.2 (SEM) awake supine and it increased to 103 mmHG ± 4.4 (SEM) ($p \leq 0.03$) in the awake Trendelenburg position. Post-induction supine MBP was 79 mmHg ± 4 (SEM) and Trendelenburg position during anesthesia increased MBP to 85 mmHg ± 4 (SEM) (NS). With regard to HR, position changes in the awake or anesthetized state did not significantly affect heart rate. PAD increases when moving from the supine to Trendelenburg position in either the awake (15 mmHg ± 1 (SEM) to 20 mmHg ± 1 (SEM) ($p \leq 0.0003$)) or anesthetized (13 mmHg ± 1 (SEM) to 18 mmHg ± 1 (SEM) ($p \leq 0.0002$)) state. CVP increased significantly when moving from the supine to the Trendelenburg position in either the awake or anesthetized state. CVP increased from 11 mmHg ± 1 (SEM) to 15 mmHg ± 1 (SEM) ($p \leq 0.0005$) awake and from 10 mmHg ± 1 (SEM) to 16 mmHg ± 1 (SEM) ($p \leq 0.0001$) in the anesthetized state. No significant changes in cardiac output were observed between positions in either the awake or anesthetized state or between similar positions in the awake and anesthetized states.

DISCUSSION: In summary, Trendelenburg position affects hemodynamic parameters in either the awake or anesthetized state . It does not significantly affect cardiac output in either state. The increases in CVP and PAD caused by Trendelenburg position, particularly when no increase in CO is observed argues against its use. The decreased epinephrine levels after induction of anesthesia in either position may reflect attenuation of pre-operative anxiety. Trendelenburg position per se does not affect serum catecholamine levels.

S275

DNA SEQUENCE OF TWO GENES CONTROLLING ANESTHETIC SENSITIVITY IN C. ELEGANS

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INTRODUCTION: We reported two mutations which alter the sensitivity of the nematode, C. elegans to certain volatile anesthetics.(1) The data indicate that mutations in these two genes, unc-79 and unc-80, change a site of action of volatile anesthetics in this animal. In order to understand this change at the molecular level, we wish to know the nucleotide sequence of the DNA of these two genes. This will allow us to determine the amino acid sequence of these genes' protein products, an important step in determining their function. We report here the progress in sequencing the unc-79 and unc-80 genes.

METHODS: The unc-80 gene was isolated by identifying a transposon insertion within the gene. This led to the identification of a 300 base pair (bp) and a 1500 bp fragment of C. elegans DNA flanking the transposon insertion. The 1500 bp fragment was used to probe genomic worm DNA to isolate a 10,000 bp (10 kb) sequence that may contain the entire unc-80 gene. unc-80 DNA was sequenced using standard techniques.(2)

The unc-79 gene is being isolated by a technique called mutant rescue. This involves microinjection of DNA into a mutant unc-79 animal. If offspring arise that are normal in halothane sensitivity, the injected piece of DNA must contain the normal unc-79 gene. The DNA is then sequenced.

RESULTS: unc-80: The fragment of the unc-80 DNA first identified by transposon tagging contains both a repetitive 300 bp piece and a unique 1500 bp fragment. There are three regions of DNA, called open reading frames (ORFs), that could code for amino acids within this 1800 bp fragment. One of them contains nucleotides with strong homology to a Drosophila transposable element called mariner.(3) The other contains sequences with homology to certain glycoproteins of trypanosomes. Sequence data for the 10 kb fragment is currently being analyzed.

We have successfully used the mutant rescue technique to obtain transformants using other genes. We have not yet identified a DNA fragment containing unc-79. However, because of the location of unc-79 in the genome we anticipate obtaining sequence data shortly.

DISCUSSION: The significance of a sequence of DNA with strong resemblance to a Drosophila transposon within a gene changing anesthetic sensitivity is not clear. The strong homology of the other ORFs of unc-80 for certain trypanosomes glycoproteins indicates this protein may function within a membrane. We are extending this sequence beyond the initial 1800 bp fragment to identify large regions of the protein product. Such information may lead to an understanding of the molecular nature of the anesthetic sites of action.

REFERENCES: 1.) Morgan PG, Sedensky MM, Meneely PM: PNAS 87:2965, 1990. 2.) Sanger F, et al: J Mol Biol 143:161, 1980. 3.) Maruyoma K, Hartl DL: Genetics 128:319, 1991.

S276

Title: EVAPORATIVE HEAT LOSS DURING SURGICAL SKIN PREPARATION

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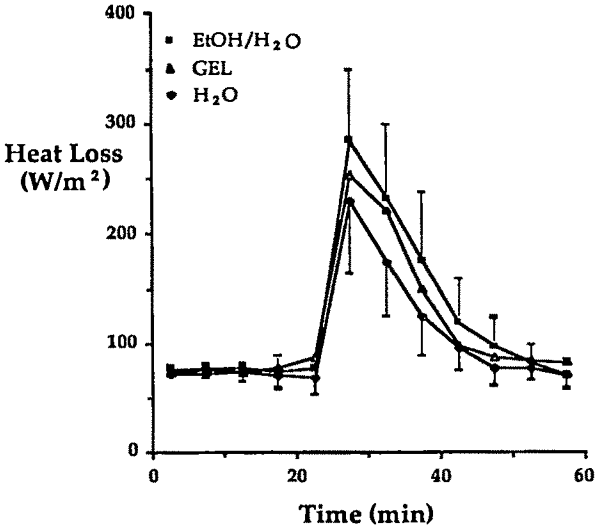
Hypothermia develops rapidly during the first h of anesthesia and has been attributed, in part, to evaporative heat loss during surgical skin preparation. We therefore tested the hypothesis that evaporation of skin preparation solution contributes significantly to hypothermia. Five healthy, unanesthetized volunteers were studied in a 22 ± 0.4°C environment. After a 25-min control period, a 10 by 25 cm rectangle on one thigh of each was painted for 10 min with three representative skin preparation solutions: 1) H_2O (similar to Betadine®); 2) 50% ethanol (EtOH) in H_2O (similar to tincture of iodine); and, 3) providone-iodine gel (E-Z Prep®). Cutaneous heat loss in W/m^2 (determined using thermal flux transducers) was measured during painting and the subsequent 25 min of drying (Fig.). These data indicate that skin preparation significantly increases cutaneous heat loss, but for a relatively short period of time. Loss with each of the three representative preparation solutions was similar.



Legend: Cutaneous heat loss during surgical skin preparation with three representative solutions.

Supported by NIH grant #R29 GM39723.

S277

ABSTRACT WITHDRAWN

S278

Title: TOLERANCE DOES NOT DEVELOP TO PROPOFOL USED REPEATEDLY FOR RADIATION THERAPY IN CHILDREN

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Deep sedation or general anesthesia are frequently required for small children undergoing high-voltage radiation therapy to ensure that they lie motionless in the radiation field. Since the introduction of propofol, we have found it to be particularly well suited to this setting. Respiratory and cardiovascular stability, and rapid emergence without residual sedation make propofol an ideal drug for radiation therapy in small children. However, radiation treatments are given one or more times per day for many weeks, and it is not known if tolerance develops to propofol with repeated administration. We reviewed our experience providing anesthesia with propofol for radiation therapy in small children to determine if tolerance developed with repeated administration.

With approval of the institutional human research review committee, the charts of children receiving propofol anesthesia without endotracheal intubation during a 1-yr period for radiation therapy were reviewed. To determine if tolerance developed or propofol dose changed with repeated exposure, linear regression analysis was performed to examine dose (normalized as per cent of first dose) as a function of number of patient exposures. Values are mean ± standard deviation and statistical significance is defined as $P<0.05$.

Propofol anesthesia was used for 134 radiation treatments for 10 children who were 2.7 ± 1 yrs old. The treatments were 13 ± 9 min in duration. Propofol was used as the sole agent for 72 treatments, and combined with ketamine or midazolam for 16 and 55 treatments, respectively. Anesthetic agents were titrated to desired effect in small bolus doses and propofol was also titrated by continuous drip for 12 procedures. For all 134 procedures, propofol dose was 4.7 ± 1.9 mg/kg or 0.50 ± 0.35 mg/kg/min. Nine patients had greater than five exposures to propofol, five patients had greater than 10 exposures, and three patients had greater than 20 exposures. For these patients, propofol dose was not related to number of exposures whether examining total dose (mg/kg) ($P=0.45$) or dose rate (mg/kg/min) ($P=0.35$) (Fig. 1).

For children undergoing radiation therapy, tolerance to propofol did not develop after repeated exposures. Propofol dose was variable among treatments, but was not affected by previous exposures to the drug.

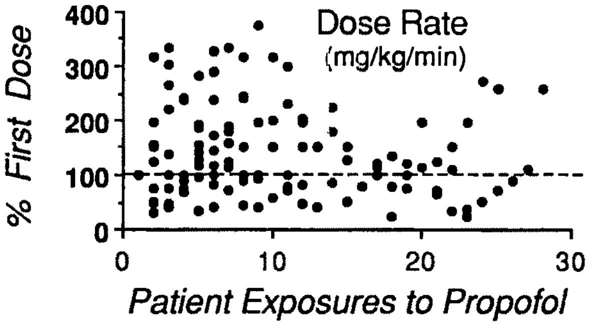

Fig.1 Propofol dose as a function of patient exposures.

S279

Title: MAXIMAL INSULIN-STIMULATED GLUCOSE AND POTASSIUM UPTAKES DURING LIVER TRANSPLANTATION

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The influence of the liver in the metabolic response to insulin has not been tested in humans, although liver disease is accompanied by marked alterations in glucose metabolism and the hormonal profile which regulates it. The liver has also been implicated in the regulation of potassium homeostasis. Liver transplantation allows whole body glucose and K^+ metabolism to be assessed in the presence of (1) a diseased liver, (2) hepatectomy, and (3) a graft liver. With IRB approval, we examined the maximal insulin responsiveness of glucose and K^+ metabolism, using a euglycemic clamp technique, in 15 patients undergoing liver transplantation at the Hospital of the University of Pennsylvania. Another 5 patients did not receive insulin. Blood samples were taken at baseline (pre-induction), anesthesia only, laparotomy, anhepatic stage, and 3 hrs post-reperfusion of the graft liver. Although basal glucose was within normal limits, plasma insulin was moderately elevated and glucagon was almost five times normal. A primed constant infusion of insulin (prime 666 mU kg^{-1}, infusion 500 mU m^{-2}min^{-1}), begun immediately following induction of anesthesia and continued throughout the operation, caused a stable plasma hyperinsulinemia (2000 uU ml^{-1}). Plasma glucagon fell by about 40% ($p<0.01$) and remained suppressed. Steady state glucose uptake (GIR, "glucose infusion rate") in the anesthetized patients was only 58% of the 14.0±1.3 mg kg^{-1}min^{-1} by 6 unanesthetized volunteers ($p<0.05$). The glucose uptake response of the patients to insulin was decreased 27% by surgical operation ($p<0.04$, Table I). Hepatectomy reduced whole-body glucose by 62% compared to laparotomy ($p<0.01$). Reperfusion of the graft liver caused a marked hyperglycemia despite the continued hyperinsulinemia and withholding of exogenous glucose for almost 2 hours post-reperfusion. Pre-incision K^+ uptake (KIR) was augmented 83% ($p<0.02$) in patients compared to the unanesthetized volunteers, partly due to total body K^+ depletion. Compared to pre-incision, insulin-stimulated K^+ uptake was decreased by 27% ($p<0.02$) during laparotomy and by 77% ($p<0.001$) during the anhepatic phase. It returned to pre-incision value after reperfusion of the graft liver. We conclude that liver disease causes an insulin resistance that is compounded by surgical operation and hepatectomy, and is not immediately reversed by liver transplantation. Post-reperfusion hyperglycemia appears to be due to either augmented glucose release by the graft liver or impaired peripheral uptake. The correlation of insulin-stimulated K^+ uptake with the presence of a liver underscores the major importance of the liver in whole-body K^+ homeostasis.

TABLE I (Mean±SEM))

Parameter	Basal	Anesth	Lapa	Hepat	Reperf
glucose	117	105	122	136	158*
(mg dl^{-1})	±17	±9	±11	±10	±20
GIR	----	8.06	5.87*	2.21*	1.83*
(mg kg^{-1}min^{-1})	----	±.94	±.85	±.88	±.79
potassium	3.8	3.4	3.6	3.9	3.5
(mEq L^{-1})	±.2	±.1	±.1	±.1	±.2
KIR	----	.22	.16*	.05*	.26
(mEq kg^{-1}hr^{-1})	----	±.02	±.03	±.02	±.06
glucagon	100	58*	59*	73*	55*
(% basal)	----	±6	±6	±13	±10

S280

Title: MECHANISM OF PLASMA LACTATE REDUCTION BY DICHLOROACETATE IN HUMANS

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Dichloroacetate (DCA), proposed as an alternative to bicarbonate for treatment of metabolic acidosis, acts by reducing plasma [lactic acid]. However, its mechanism of action is unclear. In isolated tissues, DCA activates the regulatory enzyme pyruvate dehydrogenase, to stimulate oxidation of glucose-derived pyruvate to CO_2 and decrease production of lactic acid[1]. It has also been shown to augment lactate clearance by incorporation into glycogen of incubated skeletal muscle[2]. However, the relative contribution in vivo of decreased production versus increased consumption of lactate is unknown. The purpose of this study was to determine the mechanism by which DCA reduces plasma [lactate] in humans.

Five healthy young men were studied, after providing written informed consent approved by the University of Texas Medical Branch IRB. Postabsorptive subjects, age 21-23 years, received a 5-hr primed constant infusion of 6,6-$^2H_2$ glucose and 2-^{13}C-pyruvate. The bicarbonate pool was primed with $NaH^{13}CO_3$. After the initial 2-hr basal period, subjects received DCA (35 mg kg^{-1} iv). Pyruvate, alanine and lactate kinetics were examined at 30 min intervals for 3 hrs (TABLE 1). Two days later, each subject underwent an identical procedure, except that intravenous glucose (7 mg kg^{-1}min^{-1}) was infused for the entire 5-hr protocol. Without glucose infusion, DCA increased the fractional oxidation of pyruvate from 31% to 57% ($p<0.001$). Concomitantly, DCA decreased plasma [lactate] by 40% and lactate production (Ra lactate) by 38% ($p<0.001$). Similar results were observed when glucose utilization was increased by glucose infusion. In conclusion, the principal in vivo mechanism by which DCA reduces plasma [lactate] in humans is by inhibiting its production rather than stimulating its clearance.

TABLE 1: NO GLUCOSE INFUSION (MEAN±SEM)

	Basal	DCA+120min	DCA+180min
Plasma [glucose]	86	83	81
(mg dl^{-1})	±1	±2	±2
Ra glucose	1.86	1.69*	1.66*
(mg kg^{-1}min^{-1})	±.06	±.09	±.08
Plasma [insulin]	5.3	5.0	
(uU ml^{-1})	±.7	±.5	
Plasma [lactate]	1.0	0.6*	
(mmol l^{-1})	±.1	±.1	
Ra lactate	14.2	8.8*	8.0*
(umol kg^{-1}min^{-1})	±2.2	±1.1	±0.9
Ra pyruvate	24.5	21.4	24.2
(umol kg^{-1}min^{-1})	±3.4	±1.7	±1.6
Plasma [alanine]	257	157*	
(umol l^{-1})	±22	±11	
Ra alanine-from pyr	2.99	2.20	2.38
(umol kg^{-1}min^{-1})	±.29	±.24	±.21
Pyruvate oxidation	7.26	10.43*	13.77*
(umol kg^{-1}min^{-1})	±1.34	±1.35	±1.36

[1] Whitehouse S, et al. Biochem J 141:761-774, 1974.
[2] Clark AS, et al. J Clin Invest 79:588-594, 1987.

S281

Title: KETAMINE DECREASES CALCIUM AND INCREASES MAGNESIUM BRAIN TISSUE FOLLOWING HEAD TRAUMA IN RATS

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Introduction: Ketamine (K), a well known anesthetic, also is a NMDA receptor antagonist. K previously was reported to improve neurologic outcome after head trauma (HT) (1). The mechanism(s) reponsible for these beneficial effects of K in HT and ischemia are uncertain. Calcium (Ca) accumulation in brain tissue is known to play a principal role in neuronal damage following HT (2), while magnesium (Mg) plays an important role in NMDA receptor inhibition. Accordingly, the present study was designed to determine whether K alters levels of Ca and Mg in brain tissue following HT in rats.

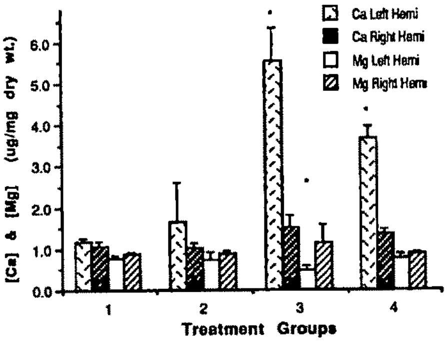
Methods: This project was approved by the Institutional Animal Care Committee. Twenty-three male Sprague-Dawley rats (235-250 g) were randomly divided into 4 groups (Gr). Gr 1 and 2 underwent sham operation and Gr 3 and 4 underwent operation and HT. Gr 1 and 3 received no treatment. Gr 2 and 4 were treated with K, 180 mg/kg ip, 1 h after HT. After sacrifice at 48 h, cortical slices were taken adjacent to the lesion on the traumatized hemisphere and from comparable sites on the nontraumatized hemisphere to measure tissue levels of Ca and Mg, by the inductively coupled plasma atomic emission spectroscopy method.

Results: With or without K treatment, HT caused a significant increase of brain tissue Ca ($p < 0.001$). However, brain tissue Ca accumulation was significantly decreased in the K treated group in comparison to the untreated group ($p < 0.0213$, unpaired t-test). HT also caused a significant decrease of brain tissue Mg ($p < 0.025$, unpaired t-test). Treatment with K restored brain tissue Mg to baseline (pre-HT) levels. Between both hemispheres Mg levels were significantly lower in the traumatized hemisphere ($p < 0.0093$, unpaired t-test) only in the untreated HT group.

Conclusion: K decreased brain tissue Ca accumulation and restored Mg levels to normal at 48 h following HT. The decrease of Ca and increase of Mg seen with K correlated well with the improvement in NSS and the decrease in infarct volume previously reported in this same model (2) suggesting that improved ionic balance may be one mechanism for K-induced improvement of neurologic outcome following HT.

References:

1. Anesthesiology (In press).
2. Neurol Res 11:169-172, 1989.



S282

TITLE: Influence of Traumatic Head Injury on Halothane MAC in Rats

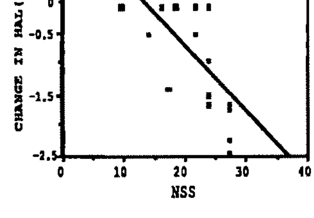
AUTHORS: Y. Shapira M.D., A. Paez, A. M. Lam M.D, E.G. Pavlin M.D.
AFFILIATION: Departments of Anesthesiology and Neurosurgery, Univ.of Washington, Seattle, WA

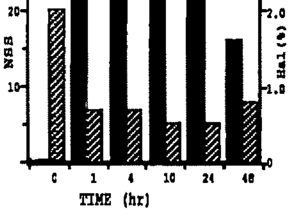
Introduction: Although the anesthetic requirement as determined by minimum alveolar concentration(MAC) is well defined in healthy patients, the influence of head injury on MAC has not been studied. Moreover, the use of neuromuscular blockade and the presence of autonomic hyperactivity following head injury often precludes assessment of depth of anesthesia. In this study we evaluated the influence of head trauma (HT)on anesthetic requirement by repetitive measurement of halothane MAC in the rat following experimental head injury.

Method: Following approval by the institutional animal care committee, 20 male Sprague-Dawley rats (200-300g) were divided into 2 groups (Gr). Gr 1 (n=14) received HT from a weight drop device following baseline determination of MAC. Gr 2 (n=6) received a sham injury. MAC was determined by applying a supramaximal pain stimulus (tail clamping) for 30 seconds and observing for somatic movements. Inspired halothane concentration(H) was adjusted by 0.4% increments up or down depending on the animal's response. At least 15 min of equilibration was maintained at each concentration. MAC was taken as the mean H between movement and nonmovement. The animals were allowed to wake up and returned to their cages between MAC determinations. In both groups MAC was determined at time 0 (baseline),1, 4, 10, 24, and 48h following HT(Gr 1). The neurologic severity score(NSS) of all study rats was determined prior to each MAC evaluation using a scale where 0 = intact neurological status and 25 = maximum functional impairment. Relationship between NSS and change in MAC was assessed using linear regression analysis and a P value of <0.05 was considered statistically significant.

Results : MAC of H in Gr 2 did not change with repetitive measurement. One animal in Gr1 died after HT and 1 died before the 48 h MAC determination. The change in NSS following HT was heterogeneous and the animals appeared to fall into two groups- mild or severe. To assess the influence of NSS on MAC, Gr 1 animals were subdivided into two groups depending on their NSS 1 hr following HT; (A) NSS < 20(mild). (B) NSS≥20(severe). In group A, there was no relationship between NSS and change in MAC. In group B, however, a statistically significant relationship between NSS and change in MAC was demonstrated.(see Figure). The time course of MAC and NSS in a representative animal in this group is also displayed.

Discussion: Our results demonstrated that the neurologic status following head trauma can significantly influence anesthetic requirement. However, the influence is not a simple one. The mildly injured animals had little or no change in MAC whereas in the severely injured animals MAC appeared to decrease as NSS increases. If these data can be applied to humans, it would suggest that anesthetic management should be planned accordingly.





S283

Title: **COMPARISON OF STAT-CRIT® WITH CONVENTIONAL HEMATOCRIT DETERMINATIONS DURING CARDIOPULMONARY BYPASS**

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Introduction: A recently reported investigation of conductivity-based hematocrit determinations in autologous blood transfusions reported a close agreement of hematocrit values derived by the conductivity of whole blood in normal samples with those determined by conventional laboratory techniques. However, it was indicated that the conductivity methods reported falsely low readings in samples of cell saver blood.[1] Patients undergoing cardiopulmonary bypass (CPB) have alterations in hematocrit for a variety of reasons; asanguinous pump prime, blood loss with intravenous crystalloid fluid replacement, and the administration of processed (cell saver device) blood. The purpose of this study was to evaluate the potential changes in accuracy of the Stat-Crit® device associated with CPB and the administration of cell saver blood as compared with conventional hematocrit determinations (Coulter counter and centrifuge hematocrit). We also examined the effects of serum electrolytes (Na+, K+, Cl-), total plasma protein, and WBC since they have been reported to effect the accuracy of the Stat-Crit®[2,3]

Methods: Twenty-nine patients undergoing CABG or valve replacement consented to participate in this IRB approved study. All patients enrolled had hematocrits determined by the Stat-Crit®, Coulter method, and centrifuge hematocrit; and Na+, K+, Cl-, total protein, and WBC, at three times: (1) preinduction of anesthesia, (2) during the rewarming period of cardiopulmonary bypass, and (3) following transfusion of all cell saver blood available after termination of CPB. All results are reported as mean ± S.D. The data was analyzed using ANOVA with $p < 0.05$ considered significant.

Results:

Table 1

	Pre-Induction	During CPB	After Cell Saver Blood
Coulter Hct	36.9±4.7	23.0±3.9	25.3±3.6*
Cent Hct	37.2±5.0	22.8±4.1	25.2±3.3
S.C. Hct	37.8±4.4	21.6±3.8	23.2±2.8*

Coulter hematocrit greater than Stat Crit Hematocrit, p< 0.01

Table 2

	Pre-Induction	During CPB	After Cell Saver Blood
Coul.-S.C. Hct	-0.8±2.7*	1.6±1.5*	2.1±1.7*
t-Protein	6.4±0.6**	3.9±0.4**	3.6±0.7**
WBC	7.6±2.3	6.7±3.8***	9.4±3.0***

*Coulter minus Stat Crit hematocrits are different at three times, p< 0.0001
**Total protein significantly higher at Pre-Induction, p< 0.0001
***WBC count increased significantly After Cell Saver Blood, p<0.005

Discussion: The results in Table 1 show that there were no differences in the hemotacrit values determined by the three methods in the pre-induction or CPB samples. Stat-Crit® hematocrit values determined after the transfusion of cell saver blood (613±212cc) were significantly lower then those determined by the Coulter method. The results in Table 2 suggest that the significant ($p<0.0001$) decrease in the total protein during CPB, and after the infusion of cell saver blood may account for the increasing inaccuracy between the Coulter and the Stat-Crit® hematocrits ($p<0.0001$). We found that the Na+, K+, or Cl- measurements did not change significantly during CPB or after the infusion of cell saver blood. The study confirms the accuracy of the Stat-Crit® compared to conventional hematocrit determinations pre-CPB. We suggest that the decrease in total protein during CPB and after the infusion of cell saver blood may account for the falsely low Stat-Crit® hematocrits.

References: 1. Anesth Analg 1990;71:541.
2. STAT-CRIT® Hematocrit/Hemoglobin Measuring Instrument Instruction Bulletin. Wampole Laboratory, 1990;p. 6.
3. Clinical Chemistry. Henry, R.J., 1974, pp. 420,643,646,720.

S284

HIGH DOSE VECURONIUM DOES NOT AUGMENT BRADYARRYTHMIAS IN CABG PATIENTS

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INTRODUCTION: Vecuronium (Vec) is a muscle relaxant commonly used for cardiac surgery due to its cardiovascular stability. However, at high doses it has been implicated as causing marked bradyarrythmias, particularly during sufentanil administration.[1,2] During sufentanil anesthesia we therefore studied the effect on heart rate (HR) of high dose Vec compared to a succinylcholine control group in order to compare the HR effects of sufentanil alone with those produced in combination with Vec.

METHODS: With ethics committee approval and patient consent, 16 adults with no known renal/hepatic/neuromuscular disease were studied. All were taking B-blockers pre-op and were premedicated with lorazepam (0.03 ± .01 mg/kg, po). Patients were then randomly assigned to one of three groups; group 1 (SxCH 1 mg/kg), group 2 (Vec 0.3 mg/kg) or group 3 (Vec 0.5 mg/kg). Anesthesia was induced with sufentanil (8 ± 2 μg/kg) and midazolam (0.06 ± .03 mg/kg). Positive pressure ventilation was used with oxygen/air to maintain $SaO_2 \geq 96\%$ and normocapnia (Nellcor capnograph). Neuromuscular blockade was measured using a Datex NMT-221 monitor (Puritan-Bennett) with surface electrodes over the hypothenar muscles and TOF supramaximal stimuli to the ulnar nerve. A Holter Monitor continuously measured HR pre and post induction for a minimum of 45 min and per cent change (%Δ) of HR was calculated. In the SxCH group this included the period following full recovery of neuromuscular blockade. Paired student's t-tests and ANOVA were used to compare changes in HR within and between groups, respectively.

RESULTS: There was a tendency for HR to decrease within each group ($p<0.10$) following sufentanil induction, however, there was no significant difference in the decrease in HR (%Δ) between groups (Table I).

TABLE I:	SxCH	0.3 Vec	0.5 Vec
(n)	4	7	5
mean HR	(pre)76±14	60±4	72±9
	(post)68±8	53±2	65±11
%Δ	-11%	-9%	-12%

CONCLUSIONS: 1) The administration of high dose sufentanil anaesthesia tended to decrease HR in all patients however, 2) there was no augmentation of the decrease in HR by the concomitant administration of high dose vecuronium.

REFERENCES: 1) Anesthesiology 64:521-523, 1986. 2) Acta Anesthesiol Scand 30:351-356, 1986.

S285

TIME FOR ONSET OF ACTION OF HIGH DOSE VECURONIUM IS COMPARABLE TO SUCCINYLCHOLINE IN CABG PATIENTS

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INTRODUCTION: Vecuronium (Vec) is a popular non-depolarizing muscle relaxant due to its cardiovascular stability. However, its ability to provide a fast and reliable degree of relaxation for endotracheal intubation, similar to succinylcholine (SxCH) is still controversial. Kaufmann[1] reduced the onset time to 94 seconds with a 0.4 mg/kg dose but no comparison to SxCH was made. Our clinical experience suggests that high dose Vec is comparable to SxCH. We therefore compared the onset time of SxCH with two different dosages of Vec in patients undergoing CABG surgery.
METHODS: With ethics committee approval and patient consent, 36 adults with no renal/hepatic or neuromuscular disease were studied. Patients were pre-medicated with lorazepam (0.03 ± 0.01 mg/kg,po) and anesthesia was induced with sufentanil (10 ± 3.4 mg/kg) and midazolam (0.06 ± 0.04 mg/kg). Positive pressure ventilation was used with oxygen/air (FIO_2=0.50) to maintain $SaO_2 \geq 96\%$ and normocapnia (Nellcor capnograph). Using a Datex NMT-221 monitor (Puritan-Bennett), a baseline electromyogram was recorded with surface electrodes over the hypothenar muscles in response to train-of-four (TOF) supramaximal stimuli delivered to the ulnar nerve at a frequency of 2 Hz every ten seconds. Patients were then randomly assigned to one of three groups; group 1 (SxCH 1 mg/kg), group 2 (Vec 0.3 mg/kg) or group 3 (Vec 0.5 mg/kg). The onset time (time of administration to time of maximal blockade) was recorded in all groups. Cardiac index (CI) was measured using a pulmonary artery catheter prior to neuromuscular relaxant administration. Anova and Student Newman-Keuls test with $p<0.05$ required for significance was used to compare groups.
RESULTS: There was no difference in CI between the three groups. (Table I) The time of onset in the 0.3 Vec group was significantly longer compared to both the SxCH and 0.5 Vec groups. There was no significant difference in onset times between the SxCH and 0.5 Vec group. Intubating conditions were excellent in all patients.

Table I:	SxCH	0.3 Vec	0.5 Vec
(n)	14	9	10
CI(l/min/M^2)	2.41±.52	2.09±.49	2.57±.75
time of onset(sec)	72±23	124±30*	86±17

* $p < 0.05$ (0.3 Vec vs. 0.5 Vec + SxCH)

DISCUSSION: This study concludes high dose vecuronium (0.5 mg/kg) significantly shortens onset time compared to 0.3 mg/kg Vec and provides a rapid and reliable degree of neuromuscular blockade comparable to SxCH.

REFERENCES: 1) Anesth Analg 67:S111, 1988

S286

TITLE: PULMONARY FUNCTION FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY

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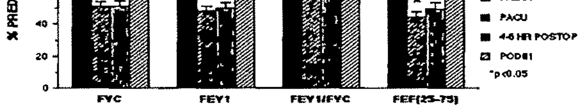
Laparoscopic surgery is becoming an increasingly popular technique for performing cholecystectomies and may be used for other abdominal procedures in the future. Although intra-abdominal procedures (e.g., open cholecystectomy) are typically associated with a restrictive pattern of pulmonary function during the early postoperative period,[1] the effects of laparoscopic procedures on pulmonary mechanics are not known. We designed a study to evaluate the effects of laparoscopic cholecystectomy on postoperative pulmonary function.

After obtaining informed consent, 31 unpremedicated ASA I-III adult patients (ages 24-84 yr) scheduled for elective laparoscopic cholecystectomy were studied according to an IRB-approved protocol. Baseline pulmonary function tests [Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV_1) the ratio of FEV_1/FVC and Forced Expiratory Flow during the middle 50% of the FVC maneuver (FEF 25-75)] were measured before the operation using a Respiradyne II® monitor (Sherwood Medical Co.). Following surgery and anesthesia, pulmonary function tests were repeated in the PACU, 4-6 hours postoperatively, and on the morning of Postoperative Day #1 (POD #1). Predicted values were based on age, height and gender using the Intermountain Thoracic Society predicted values table. Data were analyzed using ANOVA and Student's t-test to compare the changes over time; $p<0.05$ was considered statistically significant.

All patients demonstrated a statistically significant decrease in their lung volumes and flow pattern in the PACU compared to their preoperative values (figure). Although the pulmonary function tests were slightly improved on POD #1, none of the abnormal test scores had returned to their preoperative baseline values.

In patients undergoing laparoscopic cholecystectomy, a decrease in lung volumes developed in the early postoperative period without evidence of obstruction. These data suggest that there was a restrictive defect which was similar to that seen after upper abdominal procedures.[1] Although volumes returned towards preoperative values by POD #1, the time course for complete recovery of pulmonary function following this procedure is not known. Since return of pulmonary function to preoperative values requires approximately 10-14 days following intra-abdominal procedures, information regarding the time course for complete recovery following laparoscopic cholecystectomy would be valuable in determining if there is a "pulmonary sparing" effect associated with this procedure.

Reference: [1]Craig DB. Anesth Analg 60:46-52, 1981.



S287

TITLE: MATERNAL AND FETAL/PLACENTAL O_2 CONSUMPTION AND CO_2 PRODUCTION DURING SPINAL ANESTHESIA FOR CESAREAN SECTION

AUTHORS: VE Shearer, M.D., DH Wallace, M.D., AH Giesecke, M.D., and J. Wiley, RN

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We evaluated maternal and fetal/placental O_2 consumption (VO_2), and CO_2 production (VCO_2) during spinal anesthesia for cesarean section.

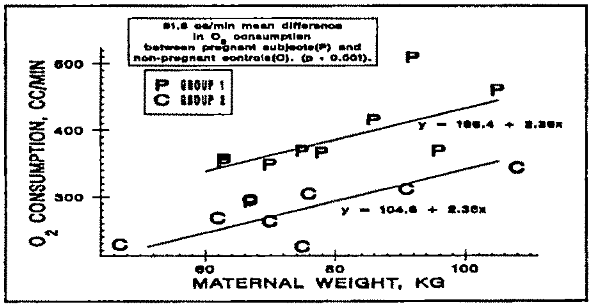
After IRB approval, 18 healthy women consented to the study. Group 1 consisted of 10 women, not in labor, with uncomplicated pregnancies for elective cesarean section. All were monitored with pulse oximetry, EKG and noninvasive blood pressure, recorded at one minute intervals. VO_2 and VCO_2 were measured with a Deltatrac metabolic monitor Model Number MBM100, (Sensormedic). In Group 1, VO_2 and VCO_2 measurements were made at five one minute intervals during five periods. Period A was baseline. Period B was after establishment of a T4 level of spinal anesthesia with hyperbaric Bupivacaine 12mg. Period C was after delivery and closure of the uterus. Period D was upon arrival in the recovery room and Period E was 24 hour post delivery. Group 2 consists of 8 nonpregnant women. Only the baseline measurement was made in this group. Women with clinical shivering, hemorrhage and excessive hypotension were eliminated from the study. Statistical techniques include students T test and repeated measures analysis of covariance.

Age, height, and weight did not differ between groups. Group 1 had a significant 32% increase in VO_2 (91.8cc/min ±18.6, p=0.0009) and a 26% increase in VCO_2 (53.08 ±9.09, 0.0006) over Group 2.(GRAPH) When compared to baseline, VO_2 was reduced 6.59% following spinal anesthesia, 16.8% after delivery and 12.9% in 24 hours. When compared to Period B, VO_2 was significantly reduced after delivery and in the recovery room.(SEE TABLE) Maternal VO2 increased 59 ±26cc/min per kg of fetal weight (p=0.02).

VO_2 and VCO_2 increases significantly in term pregnancy and decreases significantly after spinal anesthesia and delivery. We believe that the reduced VO_2 after delivery reflects the metabolic activity of the fetal/placental unit which requires a VO_2 of approximately 5.9cc/min/kg of fetal weight. These findings have clinical significance for obstetrical anesthesia.

	↓VO_2	↓VCO_2
A-B	26.9±12.1	23.9±7.6
A-C	63.1±11.6	62.6±8.3
B-C	36.2±12.0	38.7±8.3
B-D	33.7±9.5	37.3±6.1
A-E	50.9±8.8	20.2±4.5

Values: mean ±SEM. p<.01 for all values. Repeated measures analysis of covariance.



S288

Title: HEMODYNAMIC RESPONSES TO INFRARENAL AORTIC CROSS-CLAMPING IN PATIENT WITH DEPRESSED MYOCARDIAL FUNCTION: THE CLASSICAL VIEW RE-EXAMINED

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Conventionally, infrarenal aortic cross-clamping (AX) is believed to induce stress to the myocardium due to an increase of systemic vascular resistance, and consequently, patients with depressed myocardial function frequently developed signs of cardiac decompensation manifested by decreases of cardiac output (CO) and increases of pulmonary capillary wedge pressure (PCWP).[1] However, recent clinical observations[2], are contradictory to this view. In this report, we re-examined whether or not the cardiovascular responses to AX were different between the groups of patients with or without myocardial dysfunction. Methods: With the approval of the Institution Review Committee, cardiovascular responses to AX were compared between 11 patients with normal myocardial function (GI) and that of 11 patients with decreased myocardial function with ejection fraction less than 0.4 (GII) undergoing abdominal aortic aneurysm surgery. Anesthesia used was fentanyl and sufentanil. Hemodynamic examinations were done 3-5 minutes prior to AX(P) and 1, 3, 5, and 10 miutes after AX, respectively. Results: (1) There was no evidence of ST changes following AX in patients of both groups. (2) Hemodynamic responses following AX are shown in Table 1. There was no significant difference between GI and GII in any of the variables. PCWP and left ventricular stroke work index (LVSWI) did not increase significantly following AX, instead tended to decrease after 10 minutes following AX. Discussion: Our study showed that Starling mechanism is preserved during AX even in patients with myocardial dysfunction and AX is well tolerated without the sign of myocardial ischemia. Contrary to the conventional view, our observation supports the view that AX decreases myocardial demand because metabolic requirement decreases due to the separation of the part of the body.[3] References:

(1) Anesthesia. RD Miller, 2nd Ed, 1986, pp 1519.
(2) Roisen MF, et al. J Vas Surg 1:300, 1984.
(3) Shibutani K, et al. Anes Analg 72:S250, 1991.

Table 1. Mean Values and SD

		P	AX 1	3	5	10 (mins.)
MABP	GI	86 ± 10	95 ± 13*	98 ± 12*	93 ± 13*	85 ± 12
	GII	80 ± 12	92 ± 8*	91 ± 10*	89 ± 12*	81 ± 10
PCWP	GI	10 ± 4	11 ± 4	10 ± 4	10 ± 4	10 ± 3
	GII	11 ± 2	12 ± 3	11 ± 3	10 ± 2*	9 ± 2*
CI	GI	2.3 ± 0.4	2.3 ± 0.5	2.2 ± 0.5	2.1 ± 0.5	2.1 ± 0.6
	GII	2.2 ± 0.5	2.1 ± 0.5	2.0 ± 0.4	2.1 ± 0.7	1.9 ± 0.4*
LVSWI	GI	32.1 ± 7.1	33.9 ± 7.5	34.9 ± 6.5	32.0 ± 8.4	28.4 ± 9.1
	GII	29.9 ± 8.0	33.5 ± 5.7	32.3 ± 4.3	32.2 ± 8.3	27.6 ± 5.0
SVRI	GI	2726 ± 459	3061 ± 744	3300 ± 773*	3309 ± 734*	3095 ± 797
	GII	2751 ± 563	3303 ± 744*	3332 ± 621*	3333 ± 773*	3222 ± 792*

*:P<0.05 compared to precross-clamping.

S289

Title: DOES PRIOR REVERSAL WITH EDROPHONIUM OR NEOSTIGMINE INFLUENCE THE RESPONSE TO ATRACURIUM ADMINISTERED 30 MINUTES LATER?

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Introduction: Occasionally, it may be necessary to re-intubate a patient whose neuromuscular blockade has been reversed with edrophonium (E) or neostigmine (N) within 30 minutes. Which relaxant would one choose to facilitate re-intubation? Succinylcholine has been reported to have a prolonged effect following edrophonium or neostigmine.[1] However, it is widely thought that resistance to non-depolarizing relaxants may be anticipated, an issue that has not been investigated before. This report examines the effect of atracurium (75 ug/kg) administered 30 minutes following reversal of a pre-existing NMB with E or N.

Methods: After obtaining written informed consent of an institutionally approved protocol, 21 patients (ASA I or II) were studied. Anesthesia was induced with pentothal (P) and fentanyl (F) and maintained with 66% N_2O in O_2 and increments of F and P as required. Tracheal intubation was facilitated with pancuronium (70 ug/kg) (n = 10) or d-tubocurarine (0.5 mg/kg) (n = 11). The degree of NMB was measured electromyographically from the first dorsal interosseous muscle using train-of-four (TOF) ulnar nerve stimulation. Reversal of NMB was attempted when T_1 of TOF response spontaneously recovered to 25% of control using either E (0.5 mg/kg) or N (50 ug/kg) randomly allocated. At 30 minutes following reversal, atracurium (75 mg/kg) was administered and maximum twitch depression of TOF ratio (TOFR) were measured.

Results: Data were summarized as follows:

Agent:	Before Atracurium		After Atracurium	
	T_1%	TOFR	T_1%	TOFR
N	100(0)	91.6(12.0)	51.6(36.7)	13.1(11.4)
E	100(0)	65(19.3)	24.2(17.0)	3.4(4.88)

Conclusion: Contrary to our expectations, the neuromuscular blocking potency of atracurium appeared to be greater when administered shortly after reversal of pancuronium NMB. The onset of its action is characterized by considerable TOF fade. Atracurium produced a greater percentage decrease in T_1 ($P = 0.043$) and TOFR ($P = 0.049$) following E than N. The significance of this difference is unclear because the E groups demonstrated more TOF fade prior to atracurium administration ($P = 0.001$). In earlier work[2], atracurium (60 ug/kg) was found to produce only 5% single twitch suppression. Doubling the dose used in this report resulted in rapid ablation of the response in another group of patients. We can only speculate on the mechanism of this response; reversal may have enhanced a prejunctional effect of this relaxant and/or the presence of some degree of residual blockade may be contributory.

References: 1. Anesthesiology 49:188-191, 1978.
2. Anesth Analg 61:723-729, 1982.

S290

Title: MIDAZOLAM AND REGIONAL MYOCARDIAL O_2 AND LACTATE METABOLISM DURING ACUTE MYOCARDIAL ISCHEMIA IN DOGS

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Midazolam may induce in humans a significant, direct dose-dependent effect as well as an indirect, O_2-mediated effect on coronary vasculature.[1] We studied the effects of midazolam on systemic coronary and myocardial variables during myocardial ischemia, which has not been previously reported.

In 14 anesthetized (barbiturate), ventilated, surgically prepared,[2] and catheterized dogs, resting flow in the left anterior descending coronary artery (LADa) was decreased by 50% and 75% for 15 min with 1 h of normal flow in between. By arbitrary assignment, 6 dogs received midazolam, 0.3 mg/kg and then 0.05 mg/kg/min, before thoracotomy. In all dogs, heart rate (HR), electrocardiogram, LADa flow, left ventricular (LV) first time derivative, and aortic (AoP), pulmonary artery (PAP), LADa, and LV pressures were measured continuously. Before and during constrictions, cardiac output by thermodilution and regional myocardial blood flow (RMBF) by microspheres were measured; blood was sampled for analysis. Data (means ± SEM) were compared within and between groups by ANOVA.

Before constrictions (baseline), midazolam decreased HR from 167 ± 2 to 118 ± 1 beats/min, AoP from 154 ± 1 to 103 ± 0.4 mm Hg, and systolic PAP from 30 ± 1 to 23 ± 0.3 mm Hg. With midazolam and without it (control), systemic baseline values were, respectively, for LADa flow, 79 ± 2 and 115 ± 2 ml/min; for LADa pressure, 100 ± 1 and 123 ± 2 mm Hg; for HR, 118 ± 1 and 146 ± 1 beats/min; and for mean AoP, 103 ± 0.4 and 118 ± 1 mm Hg ($P < 0.05$ for each); baseline stroke volume index was higher with midazolam than without it: 27 ± 0.4 compared with 35 ± 1 ml/min/beat. During ischemia with 75% constriction, LV end-diastolic pressure was lower with midazolam than without it (4 ± 0.01 compared with 10 ± 0.3 mm Hg) as was coronary resistance expressed as the ratio between coronary (LADa) pressure and RMBF: 1.2 ± 0.2 compared with 2.0 ± 0.2 mm Hg/ml/min/100 g. During 75% constriction in the ischemic zone, lactate extraction was -130 ± 54 with and -233 ± 95% change without midazolam and O_2 consumption 1.1 ± 0 with and 2 ± 0.2 ml/min/100 g/10^3 without; also midazolam increased lactate consumption and O_2 delivery/consumption ratio.

Midazolam, by decreasing myocardial load, seemed to decrease lactate production and O_2 consumption in the ischemic zone in this canine model.

References
1. ANESTHESIOLOGY 73:A642, 1990.
2. Anesth Analg 67:124-130, 1988.

S291

TITLE: PROPOFOL REDUCES PROLONGED PACU STAY

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INTRODUCTION: For induction and maintenance of general anesthesia, propofol (P) exhibits rapid awakening, less nausea/vomiting (N/V) and possibly short PACU stay.[1-4] We examined retrospectively the duration of PACU stay in outpatients receiving P for induction and maintenance *v.* volatile anesthetics (both with N_2O).

METHODS: PACU admission records (1/89–6/89 and 1/90–6/90, with P use beginning 10/89) supplied these data: type of surgical procedure, reason for prolonged (≥2 hr) PACU stay (drowsiness [D], or N/V), P use (yes or no). Children and those receiving regional anesthesia were excluded. Two-tailed Fisher exact test or chi-square statistics provided data analysis ($P<0.05$ significant).

RESULTS: In 1990, D or N/V prolonged PACU stays of 153 / 512 outpatients. D ($P<10^{-6}$) and N/V ($P<10^{-9}$) prolonged PACU stay less frequently in patients receiving P (table 1). Did surgical procedure affect the frequency of D or N/V (taken together: D/N/V)? P decreased the incidence (table 2) of D/N/V after ortho, after gyn, and after other procedures (ENT, dental, urologic, plastic, eye). Overall 23% of ortho and 24% of gyn patients stayed in PACU for D/N/V *v.* 46% of patients having other procedures ($P=10^{-5}$).

Did PACU personnel bias these results by detaining more patients for D/N/V who received volatile anesthesia once P use became common? If so, prolonged PACU stay for D/N/V in patients not receiving P would occur more often in 1990 than in 1989. But prolonged stay decreased in these patients (N/V: 13 *v.* 17%, $P=.049$; D: 16 *v.* 27%, $P<10^{-4}$).

DISCUSSION: D or N/V often account for prolonged PACU stays.[5,6] P decreased the incidence of prolonged PACU stay due to D or N/V. PACU bias does not account for these results, despite their retrospective nature. P causes less emesis by an unknown mechanism. The lipid in P's emulsion is not antiemetic.[7] Vagotonia from eye surgery, ENT-labyrinth stimulation, and blood swallowing during oral procedures might explain the increased D/N/V compared to ortho/gyn surgery. Absence of the expected increase in N/V after laparoscopy remains unexplained. Outpatients receiving P with N_2O experience fewer PACU stays >2 hrs due to D or N/V than those receiving volatile anesthesia.

Table 1. Frequency of D and N/V leading to long PACU stay

	Total	Volatile(%)	Propofol (%)	
All adult G/A	512	261 (51%)	251 (49%)	
Drowsiness	109*	80 (74%)	29 (27%)	$P<10^{-6}$
Nausea/vom	72*	64 (89%)	8 (11%)	$P<10^{-9}$

* 28 in common, yielding a total of 153 with prolonged stay.

Table 2. Cases by procedure in patients with long PACU stay

	ALL CASES		PROLONGED STAY		
	Volatile	P	Volatile	P (% of all prolonged)	
Orthopedic	40	66	15	9 (38%)	*$P=0.0076$
Gynecologic	133	134	54	11 (17%)	*$P<0.00001$
Other	88	51	54	10 (16%)	*$P<0.00001$
Total	261	251	153†	30¶(20%)	

*Fisher exact test; †χ^2 $P=10^{-5}$, Other>(gyn=ortho); ¶χ^2 P=NS

REFERENCES:
1. Acta Anaesth Scand 34:400,1990 2. Br J Anaesth 57:725,1985
3. Anesth Analg 65:1189,1986 4. Anesthesiology 69:63,1988
5. Anesthesiology Rev XVI(1):29, 1989
6. Anesthesiology 73:A54, 1990 7. Anesth Analg 71:536, 1990

S292

Title: USE OF NONINVASIVE CEREBRAL OPTICAL SPECTROSCOPY IN PATIENTS DURING CARDIOPULMONARY BYPASS

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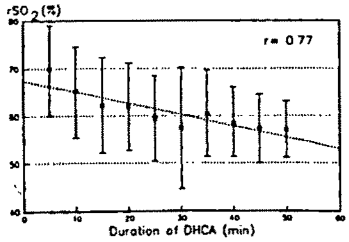
Introduction: Near infra-red in vivo optical spectroscopy penetrates the scalp, skull and brain tissue to a depth of several centimeters. Attenuation of the reflected signal is primarily influenced by the regional saturation of the hemoglobin (rSO_2) within the intracranial microvasculature, and accurately reflects mixed cerebral oxygen saturation.[1] The purpose of this study was to evaluate the utility of cerebral optical spectroscopy during CPB in patients undergoing cardiac surgery.

Methods: With IRB approval, cerebral optical spectroscopy (INVOS 3100, Somanetics, Troy, MI) was performed for the continuous noninvasive monitoring of the regional cerebral hemoglobin saturation (rSO_2) in 45 patients during CPB. Cerebral infrared spectroscopy was performed as previously described.[1] The patient-interface probe was affixed to the scalp with standard adhesives prior to induction. In all procedures use was made of moderate hypothermia (20-25°C). Deep hypothermic circulatory arrest (DHCA) was utilized in 7 patients undergoing thoracic aneurysm repair (T=15±3°C). Mean duration of DHCA was 32±12 minutes. During CPB, rSO_2 was correlated to temperature, mixed venous saturation, mean arterial pressure (MAP), pump flow and arterial blood gasses, and during DHCA, to the duration of DHCA. EEG recorded in 4 patients during DHCA was isoelectric. Data was analyzed using linear regression. P<0.05 was considered significant.

Results: Optical spectroscopy performed well at all times during CPB. As illustrated in the figure, a gradual desaturation of regional cerebral saturation over time (r=0.77, p<0.001) occurred during DHCA. Correlation with other parameters was not significant.

Discussion: Routinely measured physiological parameters poorly predict the impact of CPB on neurological function. Optical spectroscopy offers a potentially useful measure of cerebral O_2 balance even during EEG silence, and functions well during hypothermia, low flow states and even circulatory arrest.

Reference 1. Crit Care Med 19: 89-97, 1991



S293

TITLE: PROSPECTIVE ASSESSMENT OF TRAIN-OF-FOUR FADE AT 10 mA ABOVE T_4 THRESHOLD

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Introduction: It recently has been shown that the train-of-four ratio (T_4/T_1) maintains its consistency at submaximal as well as supramaximal currents.[1] However, two potential limitations have been noted when testing at submaximal current. First, especially in the context of marked depression of T_4/T_1, testing with low current may fail to elicit a detectable T_4 response. Second, at a current just above T_4 threshold, one may underestimate the height of T_4 and hence underestimate the T_4/T_1 ratio. The present study determined prospectively whether testing at 10 mA above the T_4 threshold overcomes these limitations.

Methods: With IRB approval, 60 independent data sets were obtained in 20 patients undergoing general anesthesia and nondepolarizing neuromuscular blockade. A DualStim Plus Monitor (Life-Tech Inc., Houston, TX) was applied to the volar forearm via surface electrodes, and the ipsilateral thumb was placed in an adductor pollicis force transducer. After a stable degree of blockade had been obtained, a T_4/T_1 ratio was recorded at supramaximal current. Stimulator output then was adjusted until the threshold current for the T_4 response was determined by visual assessment. The current then was increased by 10±1 mA, and a T_4/T_1 ratio was recorded. The ratio at this current was compared to that at 60 mA by paired t-test and Spearman correlation; $p<0.05$ was considered significant.

Results: The ratios generated by testing at 10 mA above T_4 threshold and at 60 mA were virtually equivalent. Their median (10-90%ile) values were 0.21 (0.09-0.89) and 0.22 (0.12-0.89), respectively (P=NS). The high degree of correlation was evidenced by a Spearman factor r=0.90. Ratios obtained at the lower current exceeded those at supramaximal current in 42% of cases and were lower in 58% of cases (P=NS).

Discussion: The data indicate that testing at 10 mA above the T_4 threshold overcomes the potential limitations associated with assessment of T_4/T_1 at submaximal current. It provides values that are consistent with those of supramaximal testing while obviating the need for higher intensity, and hence more painful, stimulation.

References

1. Anesthesiology 72:629-632, 1990

S294

TITLE: NITROUS OXIDE INCREASES MET^5-ENKEPHALIN CONCENTRATIONS IN RAT BRAIN CORPUS STRIATUM

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Introduction: Previous work has shown a selective increase in proenkephalinergic opioid peptides in the cerebrospinal fluid of dogs exposed to nitrous oxide (N_20)[1]. To study further the influence of N_2O upon the endogenous opioid system (EOS), we measured met^5-enkephalin (ME) concentrations in corpus striatum and cerebellum, brain areas respectively rich and sparse in ME, following exposure of rats to N_2O.

Methods: After Institutional Animal Care and Use Committee approval, 16 male Sprague-Dawley rats weighing 250-300 grams were placed in Lucite cages, 4 to a cage. Eight animals were exposed to a 70% N_2O/30% oxygen mixture for one hour and 8 control rats were exposed to air for an equivalent time, both at a flow rate of 10 L/min. Animals were decapitated, brains removed, microwaved for 2.5 seconds, and corpus striatum and cerebellum dissected. Brain parts were weighed and frozen at -70°C. For determination of ME, thawed parts were homogenized in 1N acetic acid and homogenates were placed in a boiling water bath for 10 minutes, centrifuged, and supernatants extracted using Sep-Pak C18 cartridges. Sep-Pak eluates were separated by reversed phase high performance liquid chromatography with a C18 column using a previously described method[1]. The separated peptides were quantitated by radioimmunoassay (RIA) using commercially available kits. All samples of the same brain part were determined in the same RIA. Protein concentrations were determined according to the Lowry method[2]. The intraassay coefficient of variation for ME was 22% and recovery was 68% (reported values are not corrected). ME concentrations in N_2O exposed and control animals were compared using Student's unpaired *t*-test.

Results: ME concentration in striata of control animals was 0.70 ± 0.09 picomoles/mg protein (mean ± SEM, n=7). In animals exposed to N_2O the concentration increased significantly to 1.25 ± 0.12 (n=8, $p<0.005$). N_2O failed to change ME concentration in cerebellum, with 0.28 ± 0.02 picomoles/mg protein (n=8) in each group.

Discussion: Our results show nearly a twofold increase in ME concentration in the corpus striatum of rats exposed for one hour to N_2O compared to air exposed rats. The striatum is an area of the brain known to be rich in the ME precursor molecule, proenkephalin. No such change is seen in the cerebellum, an expected finding since proenkephalin is sparse in this brain region. An interaction between N_2O and the proenkephalinergic branch of the EOS is suggested by these findings. This study provides further evidence for an interaction between N_2O and the EOS as one mechanism by which N_2O exerts its analgesic effects; that interaction probably consists of N_2O induced stimulation of posttranslational processing of proenkephalin resulting in increased concentrations in select brain regions of the functional neuropeptide, ME.

References:

1. Anesth Analg 70:S103, 1990.
2. J Biol Chem 193:265-270, 1951.

S295

INTRAOPERATIVE ON-LINE ST-SEGMENT ANALYSIS WITH EXTREME NORMOVOLEMIC HEMODILUTION

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Normovolemic hemodilution (NHD) is both a scientifically well founded and clinically established method to reduce the need for homologous blood. However, since the heart is the organ with the greatest $a\bar{V}DO_2$ it is the organ that limits both extent and efficiency of NHD because of danger of an inadequate myocardial oxygen supply. Therefore, this study examines the possibility to govern intraoperative NHD by continuous on-line ST-segment analysis.

This study has been performed in 140 ASA I-III-pat. undergoing an infective operation of the hip or knee. Estimated blood loss to occur was rated to be of ≥ 3.0 ltrs. All the pat. studied either completely denied homologous blood transfusion on religous reasons or agreed with its administration in danger of life, only. Intraoperative ST-segment analysis has been performed by a Siemens Sirecust-Monitor 1280 using lead II and V_5. ST-segment changes have been considered ischemic, if there were horizontal or down-sloping depressions of ≥ -0.1 mV or newly occurring elevations of the ST-segment of ≥ +0.2 mV. Statistical analysis has been performed by the unpaired Student's t-test with $P<0.05$.

Hemoglobin values prior to NHD differed significantly between the pat. of ASA-group I/II (n=77) and of ASA-group III (n=73) (Hb 11.8 ± 0.18 vs 10.8 ± 0.26 g/dl) as well as the blood volume exchanged by NHD (14.1 ± 0.5 vs 11.5 ± 0.1 ml/kg); however, the hemoglobin levels reached at the end of NHD were identical for these two groups (8.0 ± 0.5 vs 8.1 ± 0.17 g/dl). Before starting NHD 11 ASA-III pat. demonstrated ST-segment depressions, while no patient of ASA-group-I/II did so. At the end of NHD 5 ASA-I/II-pat. and 8 ASA-III-pat. showed new ischemic ST-segment changes. Continuing to substitute the blood loss with a colloid caused an additional increase in the number of pat. with newly occurring ischemic ST-segment depressions (13 pat. in ASA-group I/II and 15 pat. in ASA-group III). The corresponding Hb-level differed significantly between these pat. of ASA-group I/II and those of ASA-group III (4.7 ± 0.26 vs 6.3 ± 0.37 g/dl). 3 of these pat. of ASA-group III intraoperatively complained of chest pain, which could effectivly be treated by transfusion of blood and administration of trinitroglycerine. Routinous postoperative ECG as well as determination of the enzymes CK, CK-MB, LDH and SGOT revealed neither any serious myocardial ischemia nor even a myocardial infarction in the pat. studied; until dismission no myocardial infarction and no death occurred in this group of 140 pat.

Our results show, that it is possible to govern extreme intraoperative NHD by continuous on-line ST-segment analysis. Moreover, it is to be demonstrated, that the critical Hb-level, at which ischemic ST-segment changes occur, differs significantly between pat. of ASA-group I/II and those of ASA-group III.

S296

Title: ALL PRESSURE SUPPORT VENTILATION IS NOT CREATED EQUAL

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Introduction: Pressure Support Ventilation (PSV) applies a preselected level of positive airway pressure during the inspiratory phase of spontaneous breathing. PSV is often used to compensate for the added inspiratory work of breathing spontaneously through a tracheal tube and the demand valve of a mechanical ventilator. However, initiation of inspiration requires triggering of a demand valve, the sensitivity of which may vary among different ventilators. Thus, the work of breathing during PSV may vary between different ventilators. We compared the unloading of simulated inspiratory muscle work (WI) during PSV with three ventilators.

Methods: Spontaneous breathing was simulated with a dual-bellows lung model. One bellows was connected to the test ventilator and the other to a time-cycled, constant flow generator. The constant flow generator was used to simulate respiratory muscles by inflating one bellows, which displaced the other bellows. As the other bellows expanded, a subatmospheric pressure was created and transmitted to the test ventilator through a 5 cm H_2O/L/s resistor to simulate breathing through a tracheal tube. Gas flow was measured with a pneumotachograph and a differential pressure transducer. Another transducer was used to measure the differential pressure across the bellows inlet. Pressure and flow signals were sampled by an analog/digital converter installed in an IBM Model 70 computer. Digitized signals were used to plot pressure, flow, and tidal volume and to calculate WI. Work (mJ/L) was computed with a standard tidal volume (VT) with VT/inspiratory time ratios (VT/TI) of 0.4, 0.6, and 0.8 L/s without PSV (baseline WI) and with pressure support levels of 5 and 10 cm H_2O. Three different ventilators were studied: Bennett 7200A, Hamilton Veolar, and Siemens 900C. PSV was set to initiate with an inspiratory pressure of -1.0 cm H_2O. Work calculations were averaged from nine consecutive breaths. Percent reduction in WI was calculated by dividing WI during PSV by the baseline WI.

Results: Baseline values of WI associated with a VT of 430 ml and VT/TI of 0.4, 0.6, and 0.8 L/s were 873, 1018, and 1215 mJ/L, respectively. The percent of baseline WI unloaded by PSV of 5 and 10 cm H_2O with varying VT/TI is summarized in the table.

Table. Percent unloading of baseline WI.

PSV (cm H_2O)	5			10		
VT/TI (L/s)	0.4	0.6	0.8	0.4	0 6	0.8
Veolar	33	20	11	73	52	37
900C	41	31	20	80	63	42
7200A	42	28	16	85	63	45

Discussion: All ventilators assumed a larger part of WI as the PSV was increased. However, the percent WI unloaded during a given level of PSV decreased as VT/TI increased. We conclude that the effectiveness of PSV depends on the performance of the demand valve and the patients inspiratory flow.

S297

Title: Does Pulse Oximetry Predict Hemodynamic Compromise in Acutely Anemic Dogs?

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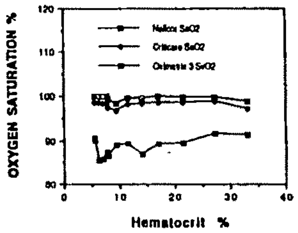
Pulse oximetry used for monitoring arterial oxygen saturation is considered standard of care. The pulse oximeter has been shown to be accurate in animal models during both oxyhemoglobin desaturation (1) as well as methemoglobinemia (2), and the results may be extrapolated to humans (1). We studied the accuracy of pulse oximetry during profound induced normovolemic hemodilution in dogs, and evaluated its monitoring potential to indicate impending hemodynamic compromise.

Eight mongrel dogs (20-25 kg) were anesthetized with pentobarbital 30 mg·kg^{-1}. The dogs were endotracheally intubated and placed on a ventilator with 100% O_2. Arterial and venous isolations were performed and catheterized for the right femoral artery and vein, left carotid and the right jugular. The right jugular was catheterized with an Abbot Opticath Fiberoptic Pulmonary Artery Catheter®. Two pulse oximeters were used (Nellcor N-100® and a Criticare Systems 504-US®) with sensors attached to the dog's tongue. Para-meters monitored were peripheral O_2 saturation and ECG, blood gases (arterial and venous), cardiac output, SvO_2, temperature, MAP, PAP, PCWP, CVP, hematocrit (Hct), and Co-Oximetry. Dogs underwent induced normovolemic hemodilution from the femoral artery catheter to a Hct of less than 10% in 300 ml aliquots at ten minute intervals and replaced simultaneously with 300 ml of dextran (6%). Acidosis, as per base deficit (6 mmol·L^{-1}), was corrected with sodium bicarbonate. All parameters were recorded every ten minutes. Results were evaluated using t-Test, with $p \leq 0.05$ considered significant.

Blood gases (arterial and venous) and pressures (MAP, PAP, PCWP and CVP remained stable. Both cardiac output and heart rate showed marked increases as hemodilution progressed. Hematocrit, total hemoglobin and arterial oxygen content decreased logarithmically. There was no statistical difference between the pulse oximeter readings as the dog became increasingly hemodiluted (see table). However, there was a significant difference noted between the two pulse oximeters ($p < 0.05$). PaO_2, SpO_2, SaO_2 (co-oximeter), SpO_2, SvO_2 (without in-vivo recalibration for change in THb) (3), did not predict hemodynamic compromise in normovolemic profoundly anemic subjects in this experiment.

References
1. Anesthesiology 1988; 68:111-114.
2. Anesthesiology 1989; 70:112-117.
3. American Journal of Physiology 1987; 253: H147-H153.

RELATIONSHIP BETWEEN HEMATOCRIT AND OXYGEN SATURATION (PERIPHERAL AND MIXED VENOUS)



S298

TITLE: EFFECT OF WARMING COVERS ON SHIVERING AFTER ARTHROSCOPY

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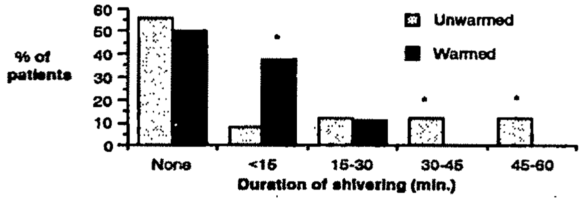
Heat loss following prolonged surgery is a common problem. However, prolonged shivering is distressingly common following even relatively short arthroscopic procedures, when large volumes of cold irrigating solution are used. Therefore, we assessed the effect of forced air warming on shivering after outpatient arthroscopy.

51 healthy, consenting outpatients undergoing knee arthroscopy were randomized to receive intraoperative warming from a Bair Hugger® or no warming (control) according to a double-blind protocol. Patients received a standardized propofol-N_2O anesthetic, with a total gas flow of 3 L•min^{-1}, and fluid replacement (unwarmed) of 5-10 ml•kg^{-1}•h^{-1}. Operating room and skin temperatures were recorded intraoperatively, as was oral temperature in the PACU. The total volume and temperature of the irrigation solution was recorded. Postoperative shivering was assessed at 15 min intervals by a blinded observer. Data (mean ± SD) were analyzed using ANOVA for continuous variables and Chi-square tests for descriptive variables, with p-values < 0.05 considered statistically significant (*).

The two groups were similar with respect to age, weight, sex distribution, ASA physical status, and duration of surgery (56 ± 26 vs 56 ± 15 min). There was also no difference in the total volume of irrigating solution used. Room temperature was similar in control (21.4 ± 1.3°C) and warmed patients (21.6 ± 1.1°C). Skin temperature was initially significantly lower in the warmed patients (34.4 ± 1.1°C) than in the control group (35 ± 0.9°C, p=0.02); however, this became similar intraoperatively and warmed patients actually had significantly higher temperatures at the end of surgery (35.6 ± 0.6 vs 35.0 ± 1.0°C, p=0.017). Postoperatively, 50% of warmed and 44% of unwarmed patients shivered. However, shivering was significantly more prolonged in unwarmed patients (p=0.02, figure). Oral temperatures in the recovery room were similar in both treatment groups (35.8 ± 0.7 vs 35.5 ± 0.6°C) and there were no differences in ambulation and discharge times between the two groups, as assessed by a blinded observer.

Postoperative shivering occurred in approximately half of all patients having arthroscopic surgery. The use of a forced air warming blanket increased intraoperative skin temperature and reduced the duration of postoperative shivering. However, discharge times were not altered. Thus, the improvement in patient comfort secondary to the decreased duration of shivering may not justify the additional cost of this technique for procedures lasting less than 1 hour.



S299

TITLE: **PIPECURONIUM-INDUCED POTENTIATION OF VECURONIUM**

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Pipecuronium (P) resembles pancuronium in its chemical structure and duration of action, but is devoid of vagolytic effects. Following initial muscle relaxation with P, vecuronium (V) may be used to extend the duration of the muscle blockade. Experience with pancuronium suggests that it may prolong the effects of subsequent doses of V (1). Therefore, we designed a randomized study to evaluate the interaction between P and V.

Fifteen healthy, consenting patients were randomly assigned to receive one of three muscle relaxant combinations, according to an IRB-approved, single-blind protocol. Group P-P received an intubating dose of P (70 $\mu g \cdot kg^{-1}$) followed by a subsequent maintenance bolus of P, 10 $\mu g \cdot kg^{-1}$. Group P-V received the same intubating dose of P, but the initial maintenance dose was V, 15 $\mu g \cdot kg^{-1}$. Group V-V received V, 0.2 $mg \cdot kg^{-1}$ for intubation, followed by V, 15 $\mu g \cdot kg^{-1}$. Supplemental doses were administered when T_1 had returned to 25% of the baseline value following the intubating dose. The time for T_1 to recover to within 25% of its baseline value following the supplemental bolus was also recorded. Neuromuscular block was monitored using a Datex Relaxograph® EMG monitor, stimulating the distal ulnar nerve and recording over the first dorsal interosseous muscle. Anesthesia was maintained using a standardized sufentanil-N_2O technique with supplemental isoflurane, 0-0.5%, as needed to maintain hemodynamic stability. Data (mean ± SD) were analyzed using ANOVA for continuous variables and Chi-square tests for descriptive variables, with p-values < 0.05 considered statistically significant (*).

The three groups were similar with respect to age, weight, height, sex distribution and ASA physical status. The onset of block (onset) following the intubating dose was faster following V than P (table). The duration (to recover to 25%) of the intubating dose was shorter following V than P. The duration of the maintenance dose of V was significantly longer when P was used for intubation than when V was used (p=0.02). The duration of V administered following P did not differ from that of P following P.

These results suggest that an initial dose of P potentiates a subsequent dose of V. This is similar to the effect of pancuronium on V. At the time T_1 returns to 25% of baseline, 80% or more of the acetylcholine receptors are still occupied by the long-acting relaxant and therefore the kinetics of this agent will have the greatest effect in determining the duration of the subsequent maintenance bolus. Thus, the degree of potentiation may decline with the administration of additional supplemental doses of V.

Group	P-P	P-V	V-V
number (n)	5	5	5
onset (sec)	280 ± 58	288 ± 50	174 ± 28*
duration (min)	96 ± 19	117 ± 15	81 ± 9*
maint. bolus (min)	44 ± 10	39 ± 6	25 ± 2*

Reference: Br J Anaesth, 57: 1063-6, 1985

S300

Title: ADVANTAGE OF RUBBER OVER PLASTIC ENDOTRACHEAL TUBES FOR RAPID EXTUBATION IN A LASER FIRE

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The occurrence of airway fires during laser airway surgery necessitates the use of special techniques to improve patient safety. It is recommended that the endotracheal tube cuff be inflated with saline. However, in the event of an endotracheal tube fire, the tube must be quickly removed. This study was designed to determine the time necessary for red rubber (RR) or polyvinylchloride (PVC) endotracheal tubes to be removed from a model airway after filling the cuffs with saline.

A Laerderal model larynx and trachea was suspended vertically. The model's larynx was intubated with either Rusch 7.0 RR or Sheridan 7.0 PVC endotracheal tubes. Six mL of saline was used to inflate the endotracheal tube cuffs. After inflation, a clamp was used to occlude the pilot tube on the RR endotracheal tubes. A 4-lb weight was then suspended from the endotracheal tube. The time to spontaneous extubation of the model trachea after unclamping the pilot tubes on 12 RR endotracheal tubes was determined. For the PVC endotracheal tubes, the times to spontaneous extubation using the 4-lb weight were determined in 12 endotracheal tubes after cutting the pilot tube and in 12 by maximum aspiration of the saline from the endotracheal tube cuff with a 10mL syringe.

A time of 0.94 ± 0.10 seconds (mean ± S.D.) was required for spontaneous extubation of the RR endotracheal tubes after unclamping the pilot tube. For the PVC endotracheal tubes, extubation occurred 3.28 ± 1.08 and 1.81 ± 0.60 seconds after cutting the pilot tube or deflating the cuff with a syringe, respectively. The mean times for each of the 3 groups were significantly different ($p < 0.05$) from each other as determined by the ANOVA.

Endotracheal tube fires are the most common serious complication of laser airway surgery. Saline should be used to fill the cuffs of endotracheal tubes used for laser airway surgery since laser contact with the cuff will release a stream of liquid. In the event of a laser-induced endotracheal tube fire, one of the first necessary steps is to quickly remove the endotracheal tube.

The present study shows that if PVC endotracheal tubes are used, deflation of the saline-filled cuff by aspiration with a 10 mL syringe is faster than cutting the pilot tube. Unclamping the pilot tube on a RR endotracheal tube resulted in the fastest time to endotracheal extubation.

S301

Title: GROWTH OF *CANDIDA ALBICANS* IN MEDICATIONS COMMONLY USED DURING ANESTHESIA

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In this study, we investigated the growth of *Candida Albicans* in 11 medications commonly used during anesthesia.

Methods

A standard colony of *Candida Albicans* was added to 20 ml of the following solutions: A 20 ml. single dose ampule of Fentanyl (Abbott Labs, N. Chicago, IL). 2) 5 ml. pre-filled syringes of preservative-free 2% Lidocaine (Abbott Labs). 3) Neosynephrine 1% in a single dose ampoule (Quad Labs, Indianapolis, IN) diluted to 100 ug.ml^{-1} with preservative-free saline. 4) Ephedrine 50 mg.ml^{-1} (Abbott Labs) from a single dose ampoule diluted to a concentration of 5 mg.ml^{-1} with preservative-free saline. 5) Atropine 0.4 mg.ml^{-1} (Elkins Sinn, Inc., Cherry Hill, NJ) from a multidose vial. 6) Succinylcholine 20 mg.ml^{-1} (Abbott Labs) from a multi-dose vial. 7) Atracurium 10 mg.ml^{-1} (Burroughs-Wellcome, Research Triangle, NC) from a multidose vial. 8) Vecuronium 1 mg.ml^{-1} (Organon, Inc., W. Orange, NJ) prepared with a diluent containing benzyl alcohol. 9) Neostigmine 1 mg.ml^{-1} (Lyphomed, Inc., Rosemont, IL) from a multidose vial. 10) Midazolam 1 mg.ml^{-1} (Hoffman LaRoche, Inc., Nutley, NJ) from a multidose ampoule. 11) D-Tubocurarine 3 mg.ml^{-1} (Squibb, Inc., Princeton, NJ) from a multidose vial. 12) Nonbacteriostatic physiologic saline. Each solution was studied in duplicate. One microliter of the innoculated solution was plated onto Sabroud Dextrose Agar plates at 0, 24 and 48 hours after innoculation. The plates and innoculated solutions were maintained at 35° and 27° Centigrade respectively. After 24 hours, the number of colony-forming units was counted on each plate.

Results

Candida Albicans was detected after innoculation in all solutions at time zero, in all except number 11 at 24 hours and in all except 6, 7, 9, 10 and 11 at 48 hours.

Discussion

This study demonstrates that only D-Tubocurarine completely inhibited the growth of *Candida Albicans* at 24 and 48 hours after innoculation. We conclude that careful technique is required to maintain the sterility of the medications commonly used during anesthesia studied here. Furthermore, once prepared, the solutions should be used promptly and then discarded.

S302

Title: PROPOFOL BUT NOT THIOPENTAL GROWS *CANDIDA ALBICANS*

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This study was designed to determine if propofol or thiopental would serve as a growth medium for *Candida Albicans*.

In part I, we determined whether the opening of 20 propofol ampoules would result in glass particles from the exterior of the ampoule falling into the emulsion. Each ampoule was painted with red fingernail polish and the contents of the ampoule were then passed through filter paper. In part II, a sample from a colony of *C. Albicans* was added to sterile vials containing 20 mL of either 0.9% saline, 1% propofol or 2.5% thiopental. A 1 μL sample of each from the 3 vials was then obtained using a precision loop and plated onto SDE agar at the following times after inoculation: 0, 3, 6, 9, 14, 18, 23, 27 and 33 hrs. The plates were then incubated at 35°C for 24 hrs. and the number of colony forming units counted.

The filtration of two of the painted ampoules revealed red glass fragments. The saline and thiopental solutions did not increase the number of colonies of *C. Albicans* by 33 hrs. The propofol, after a latent period of 14 hrs, led to the growth of *C. Albicans* at a rapid rate.

Propofol is formulated as an emulsion containing disopropylphenol in soybean oil, glycerol and egg lecithin. It contains no preservative or bacteriostatic ingredient. The Center for Disease Control has reported that during a 5-day period, 4 patients who underwent various surgical procedures at the same hospital developed *C. Albicans* septicemia or endophthalmitis(1). It was determined that a single anesthesiologist had cared for these patients and extrinsic contamination of the propofol had occurred.

Our investigation shows that glass particles from the exterior of a propofol ampoule can contaminate its contents when the ampoule is opened. Furthermore, propofol provides an excellent growth medium for *C. Albicans*. Thiopental, on the other hand, showed no growth. We conclude that the ability of propofol to grow *C. Albicans* necessitates rigorous standards of sterility in its handling. Furthermore, once drawn up, it should be used immediately and not stored.

Reference: 1. Postsurgical infections associated with an extrinsically contaminated intravenous anesthetic agent. MMWR 39:426-427, 433, 1990.

S303

Title: IS ESMOLOL CARDIOPROTECTIVE ? TOLERANCE OF PACING TACHYCARDIA IN DOGS WITH CRITICAL CORONARY STENOSIS.

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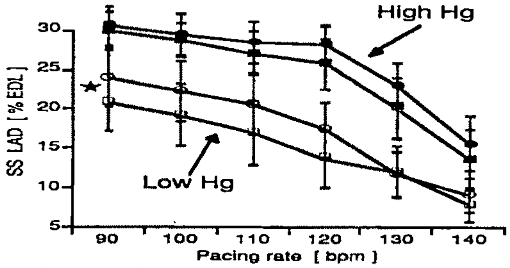
Introduction: Esmolol has been shown to decrease the infarct size in experimental occlusion of the left anterior descending coronary artery (LAD) [1], and to improve early functional recovery during coronary reperfusion [1, 2]. We hypothesized that this beneficial effect may in part be related to the decrease in heart rate during LAD occlusion and reperfusion, rather than representing an intrinsic esmolol effect.

Methods: 20 dogs, receiving humane care (NIH Publication No. 80-23, 1978) were anesthetized with halothane 0.9% and fentanyl (15 µg/kg iv; 0.3 µg/kg•min). After endotracheal intubation a thoracotomy was performed, and the heart was instrumented to measure left ventricular (LV) and central aortic pressure, cardiac output (aortic root Doppler), LAD coronary flow (Doppler), and regional myocardial function by sonomicrometry in the LAD territory, as well as in two non-compromised LV areas (basal aspect of the anterior LV wall, posterior LV wall). With atrial pacing at 90 beats per minute (bpm) a critical LAD stenosis was imposed. In 6 dogs the degree of β-blockade was assessed with isoproterenol. In 14 dogs heart rate was increased in steps of 10 bpm to a maximum rate of 140 bpm, with and without esmolol (500 µg/kg•min for 1 min, then 100 µg/kg•min) in random sequence. Esmolol was then discontinued and the dogs were hemodiluted until beginning LAD dysfunction was observed. Identical pacing epochs (with and without esmolol) were repeated at the low hemoglobin level. MANOVA ($p<0.05$) with complete block design treating pacing rate (PR) as repeated measures was used to compare the responses to increasing PR.

Results: With esmolol a 7.1±2.0 (mean±SEM) times higher isoproterenol dose was necessary to increase heart rate by 10 bpm. LV dP/dtmax was decreased with esmolol in animals undergoing the pacing protocol. Increasing PR caused a decrease in systolic shortening (SS) in all LV areas; the decrease in the compromised LAD territory, however, was more exaggerated than in non-compromised LV areas. An increase in post-systolic shortening (PSS), as well as in systolic lengthening (SL) due to increasing PR was additionally observed in the LAD territory. The responses of SS (figure), PSS, SL as well as the responses of global cardiovascular parameters to increasing PR were unaffected by esmolol. Hemodi-lution from 12.5±0.2 (HHg) to 7.4±0.2 g% (LHg) decreased SSLAD; the decrease in SSLAD due to increasing PR was more exaggerated at LHg than at HHg; esmolol had no significant effect.

Discussion: With an esmolol infusion regimen similar to that used in earlier studies [1, 2], which is expected to result in a 60-70% β-blockade [3], no cardioprotective effect could be demonstrated in the present study. An esmolol mediated decrease in heart rate rather than an intrinsic esmolol effect therefore may be responsible for the reported beneficial effects of esmolol on compromised myocardium.

References: [1] Lange et al., Am J Cardiol 51:1759, 1983. [2] Kloner et al., Am J Cardiol 56:40F, 1985. [3] Quon et al., J Pharacol Exp Ther 237:912, 1986.



SSLAD with increasing PR at high (closed symbols) and low hemoglobin (open symbols); with (■) and without (●) esmolol.
★ Significantly different ($p<0.01$) from high hemoglobin.

S304

Title: INTRAVENOUS THIOPENTAL FOR CT/MRI IN CHILDREN

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Introduction: The optimum anesthetic technique for children undergoing CT/MRI has remained elusive. Ideally, the technique should allow rapid onset of anesthesia, provide a motionless patient for either brief or prolonged scans, be titratable, allow spontaneous respiration without need for airway support, allow rapid emergence, and have minimal side effects. We prospectively studied intravenous sodium thiopental (STP) as an anesthetic for CT/MRI in children.

Methods: Following IRB approval and parental informed consent, 200 children age 2.9 ± 2.5y (range 1mo-12y) and body weight 13.9 ± 7 kg (range 3-42 kg) were studied. An initial intravenous STP dose of 6mg/kg was given to all children. Supplemental STP (1-4 mg/kg) was titrated as needed during CT/MRI at the anesthesiologist's discretion. Oxygen saturation (SpO_2) was measured continuously by pulse oximeter. The time interval from the initial STP administration until the child was positioned and ready to be scanned was estimated by the anesthesiologist. Level of consciousness was assessed 0 and 5 minutes following the scan, and every 15 minutes until awake. Fifty-six parents were contacted by telephone to determine late complications. Data are presented as mean ± SD.

Results: Patients were positioned and ready to be scanned in 3 ± 1.7 min (range 1-10 min) following administration of STP. A single dose of STP 6 mg/kg was sufficient in 30% of children to complete the scan. The mean total dose of STP was 8.5 ± 3 mg/kg (range 6-22 mg/kg). The mean duration of CT/MRI was 40 ± 21 min (range 15-160 min). The initial SpO_2 following loss of consciousness was 97 ± 2% (range 84-100%); the SpO_2 decreased below 90% in 5% of children during the scan. Tracheal intubation was necessary in two children (1%); both had coughing episodes that eventually required intubation to allow adequate scanning. Coughing occurred in 6 (3%) children, hiccoughing occurred in 21 (10.5%). 83% of children were awake (eyes open) within 5 minutes following the CT/MRI and did not require admission to the PACU. 94% of children were awake within 30 minutes and 100% within 60 minutes following CT/MRI. A single episode of vomiting occurred postoperatively in 7% of children.

Discussion: Intravenous STP is a simple, reliable method for providing anesthesia for CT/MRI in children. Children are able to be positioned and scanned shortly after induction. Spontaneous breathing is maintained and additional STP can be titrated as needed for longer scans. Most (83%) children do not require PACU admission and complications are uncommon.

S305

Title: CAPSAICIN PRETREATMENT ATTENUATES PROPOFOL-INDUCED HEMODYNAMIC EFFECTS IN ANESTHETIZED GUINEA PIGS

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Introduction: Propofol (PF) exhibits profound hypotensive properties the mechanism of which is unknown. Previous studies in isolated sympathetic ganglia suggest that PF does not function as a ganglionic blocking agent, but may act to potentiate viscerosensory synaptic input conveyed by capsaicin-sensitive visceroafferent nerves (1,2). The present study was designed to determine the role of this possible mechanism of action by studying the hemodynamic effects of PF in normal guinea pigs and in guinea pigs specifically depleted of this system of nerves by pretreatment with the C-fiber neurotoxin capsaicin.

Methods: Experiments were performed according to protocols approved by the Institutional Animal Care and Use Committee. Following induction of anesthesia with pentobarbital (PB, 50 mg/kg, i.p.), hemodynamic changes were measured via a left carotid artery catheter in response to additional intravascular doses of either PF (1.25 mg/kg, N=56) or PB (10 mg/kg, N=12). Half the animals of each study group were pretreated with capsaicin (100 mg/kg, s.c.) 5-7 days prior to performing these hemodynamic studies.

Results: In normal anesthetized animals, baseline mean arterial blood pressure (MAP) was 76 ± 2 mm Hg. PF produced one of three hemodynamic responses: hypotension (in 50%, MAP ▼ 21 ± 2 %), no change in blood pressure (in 28%), and hypertension (in 22%, MAP ▲ 15 ± 2 %). Amplitude and direction of these responses were related to the baseline MAP before PF administration ($r= -.44$). In capsaicin-treated animals, baseline MAP was decreased to 65 ± 1 mm Hg ($P< 0.05$). PF failed to produce any hypertensive response, and hypotensive responses (in 83%) were significantly attenuated in amplitude when compared to normal animals (MAP ▼ 11 ± 2 %, $P< 0.05$). There was no correlation between amplitude of individual PF responses and baseline MAP ($r= -.03$) in these animals. In sharp contrast, PB produced only hypotensive responses which were similar in amplitude in both normal and capsaicin-treated animals (MAP ▼ 15 ± 3 % versus ▼ 16 ± 4 %, $P>0.05$). With either agent tested, there was no significant change in heart rate from baseline values in both normal (245 ± 6 bpm) and capsaicin-treated groups of animals (246 ± 6 bpm).

Discussion: These data demonstrate that blood pressure responses to PF were selectively attenuated in guinea pigs pretreated with capsaicin while responses to PB remained unaffected. Taken together with previous electrophysiological findings obtained *in vitro*, these data support the hypothesis that hemodynamic changes evoked by PF *in vivo* may involve the potentiation of ongoing viscerosensory synaptic activity conveyed by capsaicin-sensitive primary afferent nerves.

References: (1) Soc.Neurosci.Abstr. 16, 59, 1990
(2) Anesth.Analg. 72, S275, 1991

Supported by National Institutes of Health (DK 17632).

S306

TITLE: OPIOID ADMINISTRATION VIA INTRATHECAL CATHETER FOR CHILDREN UNDERGOING SPINAL FUSION

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Intrathecal catheters (IT) were placed periop in 5 children undergoing spinal fusion. Morphine (0.02 mg/kg) was administered to each child intraop via catheter. Mean duration of pain relief was ± 14 hrs. Redosing was dictated by changes in pain scores. Patients with IT catheters had a higher degree of pain relief than those without IT catheters.

Patients undergoing spinal fusion experience moderate to severe pain. IT narcotics have been reported to provide analgesia for 8-72 hrs. Dosages varied from 0.01-0.025 mg/kg. This study evaluated the use of IT catheters placed intraop for repeated intermittent dosing for 48 hrs postop. The amount of additional parenteral narcotics required and occurrence of side effects were studied.

Five pediatric patients with diagnosis of idiopathic or congenital scoliosis, age range 2-16 yo, were compared to 5 historical controls. Anesthesia consisted of 60% N_2O in O_2, Sufentanil, and vecuronium. Near the end of surgery, a 17 gauge Touhy needle was inserted into the L3-4 interspace and advanced into the IT space; 20 gauge catheter inserted; and Morphine (0.02 mg/kg) administered. Redosing with morphine (0.02 mg/kg) via IT catheter was based on scores from a pain scale developed by Hannallah, et al. Catheters were utilized for 48 hrs and removed. Additional parenteral narcotics were given if analgesia was inadequate. Patients were extubated about 24 hrs postop and remained in PICU for 48 hrs.

Data collected: intrathecal morphine dose, time until redosing, parenteral analgesia requirements, and complications. Patients with IT catheters had better pain relief with lower pain scores and minimal parenteral narcotic requirements than patients without catheters. All patients required redosing within 24 hrs postop.

Children undergoing spinal fusion experience moderate to severe pain postop. Intermittent redosing allows titration of analgesia. Minimal or no side effects were encountered. It is concluded that IT catheters provide safe and efficacious analgesia for 48 hrs postop.

REFERENCES:
1. Clinical Pediatrics, 1990;29:44-48.
2. Spine, 1988;13:494-498.
3. Orthopedics, 1991;14:555-58.

S307

Title: PLASMA HEPARIN CONCENTRATION AND COAGULATION PARAMETERS AFTER SUBCUTANEOUS HEPARIN

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INTRODUCTION: Controversy exists concerning the safety of performing spinal or epidural anesthesia on a patient who has received low dose subcutaneous heparin (LDSH). This uncertainty stems from the unpredictable response of the coagulation system to LDSH.[1] In this study we examined the effect of a standard dose of subcutaneous heparin on the PT, PTT, TT and heparin concentration in patients presenting for elective abdominal surgery.

METHODS: IRB approval and informed consent were obtained. We studied 29 patients who received 5000 units of subcutaneous heparin (Hepalean, Organon) approximately one hour prior to surgery. Venous blood was drawn preoperatively, as well as 1, 2 and 3 hours after LDSH. Blood was analysed for PT, PTT, TT (using 5 units thrombin) and heparin level using the anti-factor Xa assay.

RESULTS: Highest mean PTT, TT and heparin concentrations occurred at the one hour sampling time, and are significantly increased from preoperative values (ANOVA for paired groups, $p < 0.05$) (Fig. 1). Mean heparin level at one hour was 0.028 U/ml (range 0-0.08 U/ml). There is an inverse relationship between the change in TT and Body Mass Index (Fig.2).

DISCUSSION: The therapeutic range of heparin for full anticoagulation is 0.35 - 0.7 U/ml.[2] Levels above 0.6 U/ml have been associated with serious bleeding complications.[3] In contrast to other observations,[1,3] patients in this study had levels of heparin far below this range. There is a small statistically significant increase in PT, PTT, and TT at one hour, which do not correlate with significant clinical coagulation abnormalities.

REFERENCES:

1. Cooke ED, et al. NEJM 294:1066-7, 1976.
2. Hirsch J. NEJM 324:1565-74, 1991.
3. Bonnar J, et al. Lancet 2:956, 1974.

Figure 1
Coagulation parameters

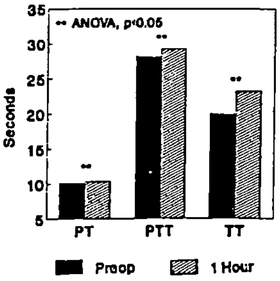
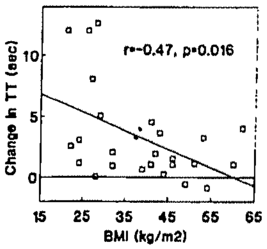


Figure 2
Change in TT vs Body Mass Index



S308

TITLE: INTRAOPERATIVE EXPOSURE TO PROTAMINE IS NOT ASSOCIATED WITH ELEVATED IgG TITRES

AUTHORS: G. Stolovitz, MD; S. Wiesel, MD; C.A. Hirshman, MD; R.G. Hamilton, MD; N.F. Adkinson Jr., MD; N.M. Sheiner, MD.
AFFILIATION: Departments of Anaesthesia and Surgery, SMBD-Jewish General Hospital, McGill University, Montreal, Canada; Departments of Anesthesiology and Clinical Immunology, Johns Hopkins University, Baltimore, Maryland.

INTRODUCTION: Anaphylaxis with preformed IgG antibodies has been implicated as a mechanism of adverse reactions to protamine[1]. Patients with peripheral vascular disease (PVD) are often exposed on numerous occasions to intravenous protamine during their procedures. We proposed to measure in this population IgG antibodies to protamine.

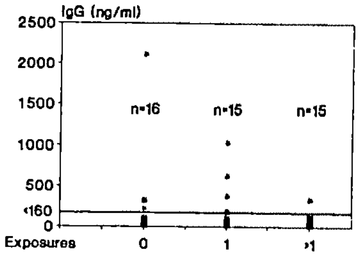
METHODS: Forty-six patients with a history of PVD were randomly selected for inclusion in this study. The number of previous documented exposures to intraoperative protamine was noted. Ten ml of blood were drawn prior to the administration of heparin or protamine. The ELISA method used detected levels of 160 ng/ml.

RESULTS: Four of 16 (25%) patients with no history of exposure to intraoperative protamine were found to have detectable levels of IgG antibody. Of the 30 patients with a documented history of intraoperative exposure to protamine, 6 (20%) had detectable levels of antibody (Chi square, $p=0.74$). Furthermore, there was no statistically significant relationship between the antibody titre and the number of exposures (ANOVA, $p = 0.46$). (Fig. 1)

DISCUSSION: In a study by Weiss[2] et al 5 of 14 non diabetic patients with adverse reactions to protamine were found to have measurable levels of IgG antibodies. These antibodies may have been naturally cross-reacting antibodies, or more likely, due to previous exposure (s) to protamine. In this study, the history of prior exposures was documented. No relationship was found between prior exposure to protamine and the presence of IgG antibodies to promatine as detected by an ELISA assay.

1. Harrow J. J Cardiothor Anesth 1988;2:225-42
2. Weiss M. NEJM 1989;320:886-892

Figure 1
IgG antibody and protamine exposure



S309

TITLE: AGING AFFECTS THE PHARMACOKINETICS OF VOLATILE ANESTHETICS IN HUMANS

AUTHORS: D Strum MD, EI Eger II MD, JD Unadkat PhD, BH Johnson MS, R Carpenter MD
AFFILIATION: Univ. of Pittsburgh, UC San Francisco, Univ. of Washington, Virginia Mason Clinic

Changes in cardiac output, lean body mass, and fat body mass due to aging suggest the possibility that aged patients may differ from young patients in the way they eliminate volatile anesthetics. To investigate the possibility that aging affects the kinetics of volatile anesthetics, we studied 7 young patients (24-37 years) and 11 aged patients (59-87 years) who underwent uneventful abdominal surgeries. We obtained prior approval from the Committee on Human Research at the University of California at San Francisco and written informed consent from each patient. Isoflurane (0.37 ± 0.01%), enflurane (0.57 ± 0.02%), halothane (0.23 ± 0.01%), and methoxyflurane (0.07 ± 0.01%), were administered simultaneously. Anesthetic concentrations in inspired (F_I),end-tidal (F_A) and mixed expired gases were measured during 30 min of administration and during 5-7 days of elimination using a gas chromatograph. F_A/F_I and F_A/F_{AO} ratios were used to define anesthetic administration and elimination respectively. Multiexponential functions were fit to the administration and elimination data using least squares regression analysis. Administration data were best fit by a 3 exponential function and elimination data by a 5 exponential function. Hybrid time constants were determined for each exponential. The effect of age on the hybrid time constants was assessed using linear regression. Total body clearance of each anesthetic was calculated by dividing the total dose of anesthetic administered by the area under the anesthetic administration and elimination curves. Linear regression analysis was used to determine the effect of age on clearance for each anesthetic. Anthropometric measurements of skin fold thickness were used to compare total body fat in the aged and young patients.

Alveolar anesthetic concentrations during administration (F_A/F_I) increased inversely proportional to the solubility of each anesthetic in blood. In contrast, anesthetic concentrations during elimination decreased coincidentally for all anesthetics. After 24 hours, anesthetic elimination slowed for the aged compared with young patients for all 4 anesthetics ($p \leq 0.05$). Total body clearance of all four anesthetics did not vary with age (p = .38-.57; $r^2 \leq 1\%$). Total body fat as measured by anthropometric measurements increased with age ($p \leq 0.00; r^2 = 68\%$).

We conclude that although aging affects the kinetics of inhaled anesthetics, the effects are small and unlikely to affect clinical practise in normal patients.

Hybrid Time Constants (min) of Alveolar Elimination

	Isoflurane	Enflurane	Halothane	Methoxyflurane
	Age 73.2 ± 3.1 yr		Weight 72.7 ± 3.1 kg	
Exponential	(n=11)	(n=10)	(n=11)	(n=8)
1	0.27 ± 0.03	0.23 ± 0.02	0.23 ± 0.02	0.09 ± 0.03
2	8.12 ± 0.52	7.62 ± 0.56	7.62 ± 0.38	8.51 ± 0.84
3	61.2 ± 8.94	72.1 ± 7.73	91.6 ± 14.4	64.4 ± 6.72
4	521 ± 59.7	559 ± 90.5	398 ± 121	588 ± 83.0
5	3704 ± 411^a	3333 ± 222^b	3846 ± 444^c	4167 ± 868^d
	Age 31 ± 1.8 yr		Weight 65.2 ± 3.0 kg	
Exponential	(n=7)	(n=7)	(n=7)	(n=4)
1	0.29 ± 0.02	0.25 ± 0.02	0.27 ± 0.01	0.13 ± 0.02
2	6.13 ± 0.41	5.99 ± 0.54	7.41 ± 0.52	8.26 ± 0.44
3	56.2 ± 2.81	57.5 ± 2.74	52.4 ± 4.20	55.8 ± 14.0
4	405 ± 36	433 ± 28	347 ± 53	356 ± 23
5	2037 ± 398^a	1942 ± 320^b	2294 ± 458^c	2353 ± 327^d

Values are mean ± SEM
a,b,c,d values are significantly different ($p \leq 0.05$)

S310

TITLE: THE EFFECT OF AGE ON NEUROLOGIC OUTCOME AFTER CARDIAC SURGERY

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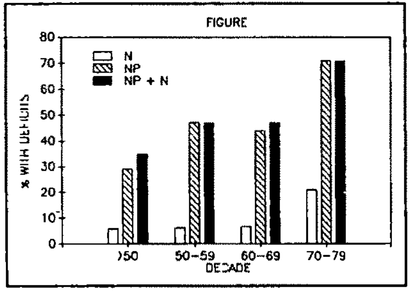
Introduction: Numerous variables contribute to the high incidence of neuropsychological (NP) dysfunction associated with cardiac surgery. Pump time (1), the number and composition of emboli delivered to the brain (2), reduced perfusion (3) and cerebrovascular disease (4) are a few of the possible risk factors contributing to negative neurological (N) outcome. However, age is considered to be a major risk factor in any review of outcome after cardiac surgery (5). We reviewed data from 68 patients (35 CABG, 33 CVR) undergoing cardiopulmonary bypass and stratified them by decade into 4 groups to determine if age was a factor in neurological outcome after cardiac surgery.

Methods: After IRB approval, written informed consent was obtained. The patients were assessed the day prior to surgery and again 7 days post surgery on 8 brief neuro-psychological tests (Trail Making Tests A and B, Grooved Pegboard - both hands, Finger Tapping - both hands, Symbol digit and a visual reaction time test). They also received a neurologic and neuro-ophthalmologic evaluation. Subjects' postoperative scores were compared to their preoperative performances and a NP test was considered to be in deficit if performance dropped by 20% from the patients preoperative score. A significant impairment was a deficit on 3 or more of the 8 tests.

Results: There was no significant difference between the CABG and CVR groups in the overall number of patients with NP/N deficits (60% vs 61%). Therefore they were combined for the purposes of this comparison. There were no differences in the pump times for either surgical category or by decade. Further, there were no difference in pump time when comparing those who had deficits vs those without (131 min. ± 41 vs 120 ± 47). When decline in only 1 NP test was used for comparison, the youngest group had a lesser event rate of 71% than the 3 older groups which averaged 85% by decade. However, when a more stringent criteria was used (deficit on 3 or more tests and/or a neurologic event) the results showed a marked difference in the number of older patients (71%) with deficit as compared to the below 70 groups (<50%) (Fig).



Conclusions: Age appears to be an important predictor of neurologic outcome in patients 70 years and older when relatively stringent evidence of neurologic trauma is used. Older aged subjects have 3 times the event rate of younger subjects on neurologic exam and almost twice the event rate on tests of memory and motor function.

References:

1. Rogers AT, et al. J Thorac Cardiovasc Surg (In press).
2. Stump DA, Stein CS, Tegeler CH, et al. J Neuroimag 1991;1:18-22
3. Prough DS, Rogers At, Stump DA, et al. Stroke 1990;21:1162-1166
4. Gravlee GP, Roy RC, Stump DA, J Thorac CV Surg 1990;99:1022-29
5. Newman SP, Perfusion 1989;4:93-100.

S311

TITLE: DOES NITROUS OXIDE(N_2O) CAUSE POSTOPERATIVE NAUSEA AND VOMITING?

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N_2O is often said to be the cause of nausea/vomiting (N/V) especially in ASC pts. The purpose of this study was to compare the incidence of N/V in ASC pts receiving isoflurane(I), N_2O-O_2, with pts receiving 4 different intravenous agents in combination with I-O_2 as general anesthesia without N_2O.

METHOD: This study was approved by the Institutional Review Board. Pts, ASA Class I - II, aged 21-81, with written consent, participated in the study. It was a double blind, third party open parallel study. Non-pregnant females, aged 18 yrs or above, with no history of N/V and needing breast biopsy under general anesthesia were recruited. One of the 5 types of adjuvant agents was randomly assigned to each pt. All groups had I - O_2 as maintenance and either thiopental (T) or propofol (P) for induction: Groups N_2O, alfentanyl(A), and T had T for induction, whereas Groups P and PA had P for induction. The pt was observed postoperatively by an evaluator who was not aware which anesthetic was administered and evaluated as follows: 0= no symptoms, 1= nausea 2= retching 3= vomiting

RESULTS: The pt's age, wt, and length of anesthesia were similar among the 5 groups.

RECOVERY TIME IN PACU (TABLE 1,2)
Group PA took the shortest time to recover in both Phase I (pt arrival PACU to Aldrete score 10) and II (pt sit up to discharge). Group T was just the opposite.

NAUSEA/VOMITING IN PACU Groups PA (3/16) and P (3/19):the least. Group T (8/19):the most. Group N_2O was next to the least.

NAUSEA/VOMITING 24 hrs. Group PA had the least N/V (1/16); Group T had the most (11/19). The other 3 groups are similar.

CONCLUSION: There is no evidence that N_2O is the sole agent to cause postoperative N/V in ambulatory surgical pts.

TABLE 1. PHASE I RECOVERY (MIN)

	N_2O	A	T	P	PA
N	18	18	19	19	16
MEAN	16.6	10.9	23.8	10.0	6.9
S.E.M.	4.3	2.9	4.5	3.2	1.8

(Differences among the groups $P = 0.01$; ANOVA)

TABLE 2. PHASE II RECOVERY (MIN)

	N_2O	A	T	P	PA
N	18	18	19	19	16
MEAN	83.8	88.8	107.7	58.6	53.0
S.E.M.	9.0	8.0	12.6	5.6	4.3

(Differences among the groups $P < 0.001$; ANOVA)

S312

TITLE: THE COMPLICATIONS AND UNEXPECTED ADMISSIONS IN AN AMBULATORY SURGERY CENTER (ASC): A 4 1/2 YR STUDY

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ATLANTA, GA 30322

INTRODUCTION

The purpose of this retrospective study was to examine the complications in our free-standing ambulatory surgery center for the past 4 1/2 years. We wanted to examine the unexpected admissions in comparison with the national incidence and also to identify the type of complications for future prevention.

METHODS

Information on consecutive patients done in the ambulatory surgery was examined. Any patient who had complications and who was admitted was noted. The types of complications were identified and categorized by the different surgical specialties and/or anesthesia. The outcome of the patient after admission and followup was recorded.

RESULTS

From January 1987 to June 1991, the total number of patients done in ambulatory surgery was 17,832. The unexpected admissions were 163 (0.91%). Causes of admission: pain 44/163 (27%); unplanned more extensive surgery or pt needing further procedures 38/163 (23.3%); bleeding postoperatively 33/163 (20.2%); unknown 13/163 (8%); pt request (no one to take care of them) 9/163 (5.5%); respiratory or cardiac complications 10/163 (6.1%); intractable nausea and vomiting(N/V) 5/163 (3.1%); urinary retention after GU procedures 3/163 (1.8%); insurance problem 1/163 (0.6%).

CONCLUSION

In our institution, unexpected admission rates were at the low end of the national average (0.1 to 5%)[1,2,3]. The majority of unplanned admissions was due to pain, more extensive surgery, bleeding, etc. Unexpected admissions due to cardiac, or respiratory complications, and N/V were rare.

REFERENCES

1. Dawson B, Reed WA. Can Anaesth Soc J 27:409, 1980
2. Meridy HW. Anesth Analg 61:921, 1982
3. Natof H: In BV Wetchler (ed),Anesthesia for Ambulatory Surgery. JB Lippincott, Philadelphia, p.321 1985

S313

Title: **AMINOPHYLLINE ACCELERATES RECOVERY FROM FATIGUE IN HUMAN INTERCOSTAL MUSCLES *IN VITRO***

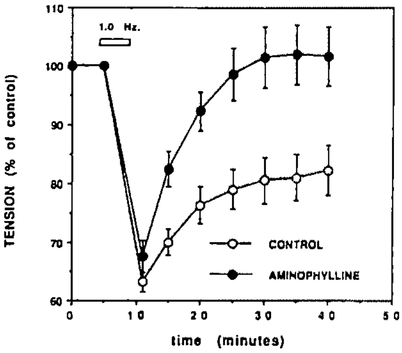
Authors: G. Suyeoka, B.A., S. Glusman, M.D., Ph.D., T. Thurston, M.D., M. Ferguson, M.D.*,
Affiliation: Depts of Anesthesia and Critical Care and Surgery,* Univ of Chicago, Chicago, IL 60637

Introduction: Respiratory muscle fatigue may be a significant component in the pathophysiological cascade leading to respiratory failure. In isolated rat diaphragm, aminophylline increases contractile tension and accelerates recovery from fatigue. The effects of aminophylline have not been studied in human respiratory muscles. In this communication we report the effects of aminophylline on human intercostal muscles *in vitro*.

Methods: After protocol approval by the IRB and informed written consent, external intercostal muscle (≈2 cm x 2 cm) was obtained from patients undergoing thoracotomy. Bundles of muscle fibers (≈10 mm in length by 2 mm in diameter) were dissected. One end of each bundle was fixed to the floor of a perfusion chamber and the other end was connected to a force transducer. The muscle was continuously perfused with oxygenated Ringer' solution plus *d*-tubocurarine post excision. Supramaximal electrical stimulation by trains (260 ms, 20 Hz) at a rate of 0.1 Hz was delivered via bipolar platinum electrodes, and the tension generated by the muscle was recorded on a pen recorder. A resting tension sufficient to maximize contractile tension was applied. Fatigue was induced by increasing the rate of stimulation to 1.0 Hz for 5 min. Recovery from fatigue was assessed by analyzing the return of tension after resumption of the 0.1 Hz stimulation rate.

Results: Increasing the rate of stimulation from 0.1 Hz to 1.0 Hz for 5 min decreased the tension generated by isolated external intercostal muscle. A slow recovery in tension was seen upon returning the rate of stimulation to 0.1 Hz ($t_{1/2}$ of recovery 24.9 min). Aminophylline (1 x 10^{-3}M) increased contractile tension (41%), and significantly accelerated recovery from fatigue ($t_{1/2}$ of recovery 8.9 min, p<.002 (t-test),n=9)

Discussion: The acceleration of recovery from fatigue in human intercostal muscle by aminophylline may be relevant in the treatment of patients with respiratory failure. In human intercostal muscles, as in rat diaphragm, the increase in contractile tension and the acceleration of recovery from fatigue by aminophylline may not share a common mechanism. The positive inotropic effect of aminophylline may be due to changes in voltage-dependent Ca^{2+} conductances, whereas the acceleration of recovery from fatigue may be mediated via competition with adenosine for adenosine receptors.



S314

Title: **RECOVERY FROM FATIGUE IS ACCELERATED BY A Na^+/H^+ IONOPHORE IN ISOLATED RAT DIAPHRAGM**

Authors: G. Suyeoka, B.A., T. Thurston, M.D., S. Glusman, M.D, Ph.D.
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Introduction: Diaphragmatic fatigue may be a significant component in the pathophysiology of respiratory failure. Muscle fatigue is associated with generation and accumulation of H^+ inside the cell. It has been proposed that the acceleration of recovery from fatigue induced by several pharmacologic agents in rat diaphragm is associated with the activation of a Na^+/H^+ antiporter in the muscle cells.[1] To test this hypothesis we investigated the effects of monensin, an ionophore that mediates exchange of Na^+ for H^+ across the plasma membrane[2] on recovery from fatigue in the isolated rat diaphragm.

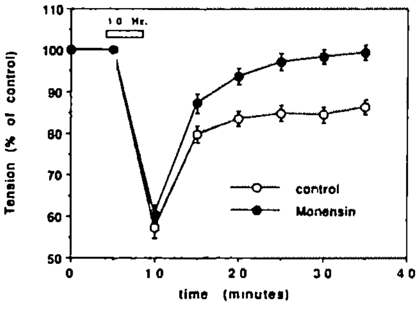
Methods: After approval by the Animal Care Committee, Sprague-Dawley rats were anesthetized with ether and medial strips of the diaphragms were removed. The costal margin of each strip was fixed to the floor of a perfusion chamber and the tendon was connected to a force transducer. The preparations were continuously perfused with oxygenated Ringer's solution containing *d*-tubocurarine. A resting tension sufficient to maximize the contractile tension was applied. The diaphragms were supramaximally stimulated via bipolar platinum electrodes at a rate of 0.1 Hz and contractions were monitored on a chart recorder. Fatigue was induced by increasing the rate of stimulation to 1.0 Hz for 5 min. Recovery from fatigue was assessed by analyzing the recovery of tension after resumption of the 0.1 Hz stimulation rate.

Results: Electrical stimulation of rat diaphragm at 1.0 Hz for 5 min reduced the tension that the muscle generated (fatigue). There was a gradual recovery from fatigue in the muscle upon return of the rate of stimulation to 0.1 Hz. Monensin (1 x 10^{-5}M) significantly accelerated recovery from fatigue in the diaphragm without affecting the degree of fatigue (p<.001 (t-test).

Discussion: Several mechanisms participate in the regulation of intracellular pH in the fatigued muscle. The acceleration of recovery from fatigue in rat diaphragm by monensin, a Na^+/H^+ ionophore, suggests that recovery from fatigue and restoration of intracellular pH via Na^+/H^+ exchange across the muscle membrane may be closely related. The effect of monensin on recovery from fatigue is similar to the effect of non-ionophore pharmacological agents that activate the Na^+/H^+ antiporter.[1] These results may be significant in the search for agents capable of reversing respiratory muscle fatigue.

References:

1. Anesthesiology 71: A1118, 1989
2. J Gen Physiol 83:341-369, 1984



S315

Title: **COMPARISON OF VASODILATION BY HALOTHANE ON NORMOTENSIVE AND HYPERTENSIVE RAT AORTA**

Authors: J.F. SZOCIK, M.D., R.C. WEBB, Ph.D., D.W. WILDE, Ph.D.

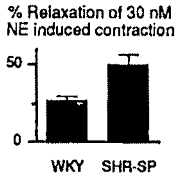
Affiliation: UNIVERSITY OF MICHIGAN MEDICAL CENTER, DEPT. OF ANESTHESIA, ANN ARBOR, MI

Introduction. Hypertension is common in patients undergoing anesthesia and these patients respond differently to anesthetics than normotensives. Hypertensive patients have a greater decrease in mean arterial pressure (MAP) and systemic vascular resistance (SVR) than normotensives.[1] A similar drop in the MAP in hypertensive rats exposed to halothane has also been shown.[2] This study describes the effects of halothane (H) on the norepinephrine (NE) - induced contraction of vascular smooth muscle (VSM) of normotensive (WKY) and hypertensive (SHR-SP) rats.

Methods. Descending thoracic aortae from age-paired male SHR-SP and WKY rats were excised under phenobarbital anesthesia (50 mg/kg ip), placed in 1.6 mM Ca^{2+} PSS and dissected free of fat and connective tissue. Pairs of upper thoracic aortae (one SHR-SP, one WKY) were cut into 5 mm rings, denuded of endothelium and mounted in muscle baths. Muscle tensions were measured with Grass FT03 force transducers and records displayed on a Grass polygraph. Rings were equilibrated in PSS gassed with 95%/5% O_2/CO_2 for 1 hr under 3 g resting tension at 37°C. NE, 30 nM, was added to the bath to induce contraction. At peak response, H (3%) was bubbled into the bath and the effect on tension recorded.

Results. Results (mean ± SEM, n=5) are expressed as mg of tension generated (*see* Table) and % relaxation (*see* Figure).

	Control	3% H
WKY	1043±158	752±109*
SHR-SP	1328±155	676±130*



% Relaxation of 30 nM NE induced contraction†

Discussion. The SHR-SP aortic VSM is more responsive to H than the WKY. This correlates with clinical studies in humans and whole animal work in rats and establishes part of this difference as being a direct anesthetic effect on the hypertensive VSM. NE induces contraction by release of internal stores of Ca^{2+} and increased membrane permeability to Ca^{2+}. These observations support the idea that hypertension involves alterations in cellular calcium homeostasis and that anesthetics affect this differently in hypertensive animals. An increased NE responsiveness of hypertensive aorta was observed although comparison of control values between WKY and SHR-SP did not reach significance.

References.

1. *Brit J Anes;* 43,122-137, 1971.

2. *Anesth Analg;* 64:136-142, 1985.

*Significant at p<0.02 by paired t-test.

†Significant between WKY and SHR-SP at p=0.009 by unpaired t-test.

S316

TITLE: CORE TEMPERATURE CHANGES DURING ORTHOTOPIC LIVER TRANSPLANTATION (OLT)

AUTHORS: M Tabatabai, MD, Y Kang, MD, H A Tabatabai, BS, A Navalgund, MD, H Kunkel, MD, K Wong, MD

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Introduction: Intraoperative hypothermia occurs commonly during OLT, not only because of prolonged duration of operation, but also because of the veno-venous bypass (VVBP), and reperfusion of the cold transplanted liver. These two events may not alter core temperature to the same extent at different sites. The purpose of the present study was to compare esophageal, rectal and pulmonary arterial temperatures (ET, RT and PAT respectively) during OLT, and to contrast the magnitude of the temperature change on initiation of VVBP and liver reperfusion at those three sites.

Methods: Twenty two patients, aged 45±11 years (mean ± SD), undergoing OLT were included in this study. Anesthesia was induced with etomidate and maintained with fentanyl, isoflurane and vecuronium. The ET, RT and PAT were measured continuously. Paired t-test and ANOVA were used to analyze the data. P<0.05 was considered significant.

Results: The results are presented in the Table. The ET and PAT were less than the RT before VVBP and liver reperfusion, and while the differences were numerically small, they were significant (P<0.01). After initiation of the VVBP (left femoral vein and portal vein to left axillary vein), the temperature decreased at all the measured sites, but the greatest drop was in the PAT; a decrease of 2.9°C within 1-2 minutes (P<0.001). The decrease, however, was transient and at 5 minutes after VVBP, the decrease was 0.4°C. The drop in the ET and RT after VVBP was slight (0.3°C), but significant (P<0.01). Upon liver reperfusion, the temperature decreased at the measured sites, but here too, the greatest drop was in the PAT; a decrease of 2.8°C (P<0.001). This drop was also transient such that 5 minutes after reperfusion, it was 0.5°C. The drop in the ET and RT after reperfusion, although numerically small (0.4° and 0.3°C respectively), was significant (P<0.01).

Discussion: The venous blood going to the right heart and pulmonary artery is cooled by the priming solution in the pump during VVBP, and by the cold grafted liver upon reperfusion, thus affecting the temperature of the right side of the heart and pulmonary artery differentially compared with other sites in the body. Liver reperfusion has been associated with cardiac rhythm changes of varying severity and hemodynamic instability. The cardiac cooling that occurs upon liver reperfusion may have a contributing role in the development of these complications.

TABLE (The values are mean ± SEM in centigrade)

	ET	RT	PAT
Before VVBP	34.7±0.2	35.2±0.15	34.9±0.18
2 min later	34.4±0.2*	34.9±0.2*	32.0±0.25**
5 min later	34.4±0.2	34.9±0.2	34.5±0.2
Before reperfusion	33.7±0.23	34.5±0.25	33.8±0.23
2 min later	33.3±0.25*	34.2±0.26*	31.0±0.28**
5 min later	33.4±0.25	34.1±0.25	33.3±0.25

*: P<0.01 **: P<0.001

S317

Title: FIBEROPTIC EVALUATION OF SMALL AIRWAYS WITH ACUTE RESPIRATORY FAILURE DURING MECHANICAL VENTILATION

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INTRODUCTION: Pulmonary barotrauma as pneumothorax and pneumomediastinum has been defined as the consequences of mechanical ventilation. However, the changes in the small airways due to mechanical ventilaton were only reported at autopsy[1]. Recent technology developed a fine fiberoptic bronchoscope of 1.8mm in outer diameter, which allowed us to evaluate the small airways[2]. We observed the small airways of acute respiratory failure under mechanical ventilation by using 1.8mm fiberscope, and examined whether the bronchiolectasis and other changes were identified in small airways during mechanical ventilation.

METHODS: This study was prospectively carried out in 10 patients (17 examinations) who were mechanically ventilated due to acute respiratory failure in the intensive care unit. All patients were informed of the study. Endoscopic examination of the small airways was performed by using the fiberscope of 1.8mm in outer diameter (Olympus BF-1.8T, Tokyo, Japan). The peripheral airways of 2mm or less in diameter can be observed by the fiberscope. To evaluate the relationship between the endoscopic findings and ventilatory factors, the duration of mechanical ventilation, FIO2, PEEP and PaO2 were compared among the cases.

RESULTS: Ectasis was found in 7 examinations and pallor in 8 examinations. Secretion, pigmentation, and stenosis or collapse were observed in 7, 5 and 4 examinations, respectively. Duration of mechanical ventilation in patients with ectasis was 17±9 days which was significantly longer than that without ectasis 9±5 days. There was no difference in the duration of mechanical ventilation between with and without pallor and there were also no differences in FIO2, PEEP and PaO2 between with and without ectasis or pallor.

DISCUSSION: Morphological changes of small airways such as ectasis and pallor suggest the possible barotrauma in the patients on mechanical ventilation. Bronchiolectasis was most likely depend on the duration of mechanical ventilation.

REFERENCES:

1.Endoscopic observation of peripheral airway lesions. Chest 93:228,1988
2.Bronchiolectasis- a complication of artificial ventilation. Br Med J 285:931,1982

S318

Title: THE HYPNOTIC CONCENTRATION OF THIOPENTAL WITH AND WITHOUT FENTANYL

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Introduction: Thiopental and fentanyl are commonly combined for the induction of anesthesia The exact interaction of these two drugs to produce hypnosis has not been well documented. In this study we evaluated the effect of an analgesic concentration of fentanyl on the plasma concentration of thiopental to induce sleep.

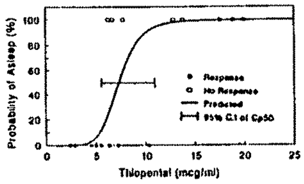
Methods: Following IRB approval and written informed consentt 46 ASA I or II unpremedicated patients were studied. In all patients thiopental was infused using a pharmacokinetic model driven infusion device (CACI) that enables intravenous drugs to be infused to a desired plasma concentration[1]. Patients were randomly assigned to receive a predetermined concentration of thiopental which was maintained for 10 minutes. Asleep was defined as an inability to respond at 10 minutes to a verbal command to open their eyes. In 22 of the 46 patients fentanyl was simultaneously infused by CACI to a desired plasma concentration of 1 ng/ml (an effective analgesic level) and the same assessment was made at 10 minutes. Blood samples for thiopental and fentanyl concentrations were taken 5 and 10 minutes after the start of drug administration. The thiopental and fentanyl concentrations in the samples taken at 5 and 10 minutes were compared. Patients in whom these were not within ±30% of each other were excluded from the calculation of the plasma concentration at which 50% of the patients were asleep ($Cp50_{asleep}$). The $Cp50_{asleep}$ and its 95% confidence limit was calculated using a maximum likelihood solution to a logistic regression model.

Results: The concentrations at which the patients were and were not asleep, with and without fentanyl, are presented in the figure. The Cp50 asleep for thiopental alone (n=17) was 7.32 (95% C.I. 5.5-11.0) μg/ml and in the presence of fentanyl (measured concentration 1.3±0.5 ng/ml) was 7.22 (95% C.I. 4.8-10.2) μg/ml (n=17).

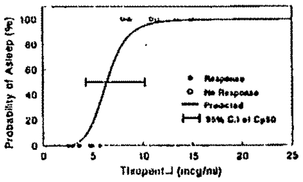
Discussion: The methodology used in this study insures that the variability due to pharmacokinetics and pharmacodynamics resulting from bolus dose response strategy is accounted for. When equilibration between plasma and effect site concentration has occured fentanyl does not alter the hypnotic concentration of thiopental.

References: 1) Glass PSA, et al. Anesthesiology 73: 1082-90, 1990.

Thiopental Cp50 (Asleep)



Thiopental plus Fentanyl (1.27 ng/ml) Cp50 Asleep



S319

TITLE: PROPHYLAXIS OF DURAL HEADACHE - EPIDURAL SALINE BOLUS VERSUS INFUSION

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Introduction. Epidural analgesia is an accepted technique for providing pain relief during labor and delivery. One potential complication is puncture of the dura by the large epidural needle. Untreated, this leads to a postural headache in 50-70% of cases.[1] Performance of an early epidural blood patch has been advocated, but because of potential side effects is usually reserved for treatment of an established headache.

Epidural saline has been shown to be an effective and safe prophylaxis against post dural puncture headache.[1,2] Bolus injection and infusion have both been shown to reduce the incidence of spinal headache, but they have not previously been compared.

Method. Following institutional ethics committee approval, and written informed consent, thirty patients suffering accidental dural puncture with a 17g Tuohy needle were randomly assigned to one of two groups. All patients had an epidural catheter inserted at another interspace and epidural anesthesia was continued. After delivery, group 1 received a bolus of 0.9% NaCl over 5 minutes to a maximum volume of 30 ml or until the patient felt discomfort in the back. This was repeated 3 times at 6 hourly intervals. Group 2 received a continuous epidural infusion of 0.9% NaCl via a standard (10 drops per ml) IV administration set.

A second investigator, unaware of the study groups, interviewed the patients daily until discharge and at 7 days to determine the occurrence of headache, or any other symptoms. Postural headache was treated with analgesics, intravenous caffeine or a blood patch as necessary.

Results. There was no difference between the groups for age and demographic factors. The total volume of saline administered was significantly greater in the infusion group (p=0.0004). 5 patients randomised to group 1 and 2 in group 2 required cesarean delivery. Typical spinal headaches occurred in 5 of the 15 patients (33%) in each group. However, conservative analgesic therapy cured most of the headaches of patients in group 2. In the patients who delivered vaginally, 4 of 10 in the bolus group compared with 1 of 13 in the infusion group needed a blood patch.

Discussion. Both methods of administration of epidural saline reduce the incidence of spinal headaches. A lower rate of blood patch (not statistically significant) occurred in the infusion group. Not all epidural infusions ran for the full 24 hr. period, but a greater mean volume was delivered by this means. Patient, nurse and medical staff acceptance was greater with the bolus technique, and there is as yet insufficient evidence to recommend infusion over bolus.

References.
1. Br J Anesth 1972, 44:598.
2. Anesth Analg 1973, 52:228.

S320

TITLE: AMBULATORY ANESTHESIA FOR AUTOLOGOUS BONE MARROW HARVESTING

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INTRODUCTION: Bone marrow harvesting (BMH) from autologous donors is usually performed on in-patients; recently, however, we have begun to perform these procedures in our Surgical Day Hospital. We present here our experience with BMH performed on outpatients.

METHODS: We considered for review the first 63 out-pts who underwent autologous BMH. Relevant data was collected from the pre-anesthesia evaluation, the intra-op record, the PACU record and from the post-op call made the day following surgery.

RESULTS: 53 charts were available for review. Mean age was 33.9 ± 1.4 SE. 43.4% of the pts were female and 56.6% were male. The disease process was: Hodgkin's (34.0%), Leukemia (26.4%), Non Hodgkin's Lymphoma (18.9%), Testicular Ca (13.2%), or Metastatic Breast Ca (7.5%). The pts received general endotracheal anesthesia for the BMH and were ASA II (20.8%) or ASA III (79.2%). Anesthesia was induced with propofol 2.0-2.5 mg/kg and fentanyl 1-1.5 $\mu g/kg$ and maintained with 70% N_2O in O_2 and continuous propofol infusion. 1 hr prior to the end of the case ketorolac 60 mg IM was given to provide post-op pain relief. Duration of the procedure and length of PACU stay are listed below. Each pt had 10 cc/kg of marrow harvested, and this was replaced cc for cc with colloid (Hespan). Pts also received maintenance fluids with a balanced salt solution.

Of the first 63 pts in our series only 1 (1.6%) required hospital admission. In the PACU 3.8% of pts had transient dizziness and 5.7% of pts vomited. The single admission was a neutropenic leukemic pt who developed a temp = 40C in the PACU. Fever work-up was negative and he was discharged home several days later. Only 10% of the pts who received ketorolac intra-op required pain medication in the PACU prior to discharge.

We reached 92.5% of the pts at home the next day and found that 6.1% of them had at least 1 episode of vomiting. Only 36.7% of pts took the tylenol with codeine that was prescribed. The remainder of pts did not require any narcotic at home.

DISCUSSION: Our data shows that autologous BMH is an acceptable ambulatory surgical procedure that results in a very low post anesthesia complication rate. Indeed only 1 pt required hospital admission for a complication probably related to his disease process and not the procedure itself. Also, post-op pain is easily controlled. We attribute the successful outcome to appropriate fluid replacement, and the intra-op use of the non-narcotic analgesic ketorolac for post-op pain management which prevents the prolonged drowsiness, hypotension, nausea and vomiting that can accompany the use of narcotics in the PACU.

BMH duration	**110.6 mins ± 3.2 SE**
PACU I duration*	**119.1 mins ± 7.0 SE**
PACU II duration**	**104.6 mins ± 8.5 SE**
Total PACU Time	**223.7 mins ± 10.2 SE**

*** monitored in beds**
**** off monitors, in lounge chairs, taking po's**

S321

TITLE: THE EFFECT OF AGE ON RECOVERY OF PULMONARY FUNCTION AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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AFFILIATION: Departments of Anaesthesia, Medicine and Surgery, SMBD-Jewish General Hospital and McGill University, Montreal.

INTRODUCTION: Patient recovery after laparoscopic cholecystectomy (LC) is quick. We studied the effect of patient age on the recovery of pulmonary function (PFTs).
METHODS: Institutional approval and informed consent were obtained from 14 adult patients scheduled for LC. All patients were nonobese, ASA I or II, and free of pulmonary disease. Patients were divided into two groups on the basis of age: Age <50 (n=7), Age> 50 (n=7). All patients received similar anesthetics consisting of sufentanil 0.25 mcg/kg/hr and isoflurane 0.25-0.5% in 70% nitrous oxide.

PFTs consisted of the forced volume in one second (FEV_1) and the forced vital capacity (FVC). These were obtained preoperatively and 1, 6, and 24 hours postoperatively with the patient alert and pain-free. Repeated measures ANOVA was used to compare postoperative FEV_1 and FVC with the preoperative values. ANOVA for independent groups was used to compare values between groups. P<0.05 was statistically significant.
RESULTS: All postoperative FEV_1 and FVC values were significantly decreased compared to the preoperative values and significantly lower in the Age> 50 group compared with the Age <50 group at 6 and 24 hours (Figs 1&2).
CONCLUSIONS: PFTs (FEV_1 and FVC) remain abnormal for 24 hours after a LC. The recovery of PFTs at 24 hours after LC is less complete in patients older than 50 years of age.

Figure 1
Effect of Age on Recovery of FEV1

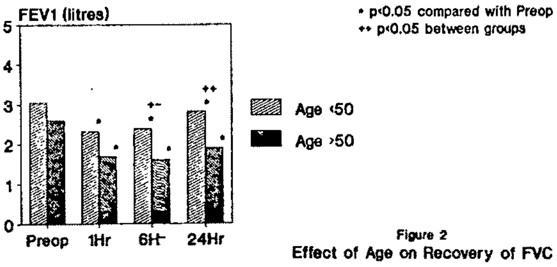
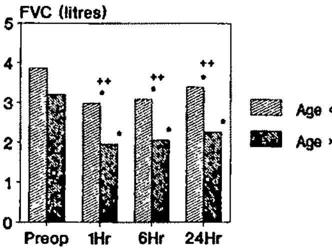


Figure 2
Effect of Age on Recovery of FVC



S322

TITLE: SUPPRESSIVE EFFECTS OF NEUROTENSIN ON FENTANYL-INDUCED MUSCLE RIGIDITY IN THE RAT

AUTHORS: M.Y. Tsou, M.D., P.W. Lui, M.D., Ph.D., T.Y. Lee, M.D., *S.H.H. Chan, Ph.D.
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Neurotensin (NT) is a tridecapeptide that is widely distributed in the brain[1] and is known to have many physiologic functions. It is generally believed that, as a neuromodulator, NT may alter the activity of other neurotransmitters or chemicals in the central nervous system [2]. The present investigation was a further study of this modus operandi of NT, in which we used fentanyl-induced muscle rigidity as our experimental index.

We used adult, male Sprague-Dawley rats (200-300 g) under ketamine anesthesia (100-120 mg/kg, i.p.), and with control of respiration, body temperature, and end-tidal CO_2. The right femoral artery and vein were cannulated with catheters filled with heparinized saline for measurement of systemic arterial pressure and for administration of fentanyl[3]. A 25-gauge stainless-steel cannula was implanted stereotaxically into the left lateral cerebral ventricle. Intracerebroventricular (ICV) injection (5 µl) of saline (NS; n=7), NT (15, 30 or 60 nmol; n=7 per group), NT (60 nmol) plus normal rabbit serum (NRS, 1:80; n=7) or NT (60 nmol) plus NT-antiserum (ANT, 1:80, n=7) was carried out by inserting a 27-gauge injector into the guide cannula. Following a 10 min baseline recording, the rats were given fentanyl (100 µg/kg, i.v). Fentanyl-induced muscle rigidity was evaluated by the electromyographic (EMG) activity from the caudal lateral extensor muscle (CLE) and gastrocnemius muscle (GC). We first quantified the EMG activity by averaging the integrated signals (every 10 s) recorded over a set time interval (6 datum points/min). These averaged values were normalized as a percentage of the predrug control to minimize interanimal variation. The effect of various pretreatments on the EMG activity from CLE and GC muscles was assessed statistically by two-way ANOVA followed by the Student-Newman-Keuls test for a posteriori analysis of individual means at various postinjection time intervals. A p value < 0.05 was taken to indicate statistical significance.

Intravenous injection of fentanyl consistently promoted a significant increase in EMG activity from both CLE and GC muscles. This implied muscle rigidity was antagonized appreciably by prior ICV administration of NT in a dose-dependent manner (Fig. 1 . The specificity of this antagonism was confirmed when ICV injection of NT+ANT failed to produce any blunting effect on fentanyl-induced EMG activation (Fig. 2).

These results indicate that NT may interact with the µ-opiate receptors in the brain to elicit its antagonizing action on fentanyl-induced muscle rigidity. The mechanism of interaction awaits further investigation.

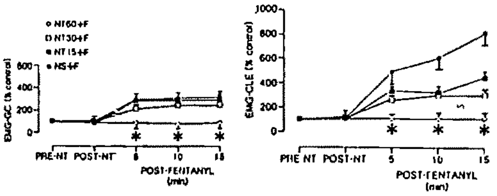

Fig. 1. Values are means ± SEM. Pre-NT, before ICV neurotensin injection; Post-NT, after ICV neurotensin injection. * $p < 0.01$ vs NS+F.

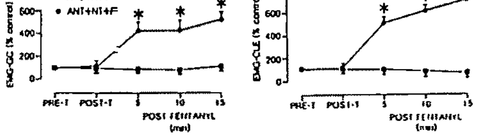

Fig. 2. Values are means ± SEM. Pre-T and Post-T represent before and after ICV injection of NRS+NT+F or ANT+NT+F respectively. * $p < 0.01$ vs ANT+NT+F.

S323

TITLE: LEFT VENTRICULAR FUNCTIONS ARE NOT IMPAIRED AFTER LUMBAR EPIDURAL ANESTHESIA IN YOUNG CHILDREN

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Introduction: Mimimal hemodynamic changes are unique features of the epidural anesthesia in young children[1, 2)]. However, effects of epidural anesthesia in this age on left ventricular functions are not known . We evaluated the left venticular functions following lumbar epidural anesthesia by echocardiography.

Methods: The study was approved by the Ethics Committee of the hospital and parental informed consent was obtained. Ten ASA I unpremedicated children scheduled for elective inguinal hernia repair were studied. Age and weight of the patients were 11.7±15.1 Mo. and 8.5±3.6 kg (Mean±S.D.). Anesthesia was induced by N_2O, O_2,and inhalational agents. The trachea was intubated following vecuronium 0.1mg/kg iv, and the lungs were mechanically ventilated in order to keep $ETCO_2$ at normal range using 50% N_2O and 1% end-tidal enflurane . Then, 0.75ml/kg of plain 0.25% bupivacaine were injected into the epidural space through $L_{3/4}$. HR, BP were measured by Dinamap™ 1869 and echocardiography were obtained by Aloka™ SSD-280 before and, 5 min.,10min.,25 min. after the epidural anesthesia. The values before epidural anesthesia were compaired with the values after epidural anesthesia using ANOVA and paired t-test. P value less than 0.05 was considered significant.

Results: Analgesia levels were up to Th 7, 8. Slight decrease in HR and systolic BP was obsereved following epidural anesthesia. However, there were no significant changes in echocardiographic indicies of left ventricular functions.

	before Epi.	5min.	10min.	25min.
HR(bpm)	130±14	127±19*	124±20*	108±42*
SP(mmHg)	84± 8	78± 9*	74±10*	72±11*
LVEDD(mm)	30.8±4.7	31.2±4.4	31.3±5.1	31.8± 4.9
LVESD(mm)	22.6±4.0	23.0±4.3	23.7±5.2	24.1± 5.3
LVSF(%)	26.8±5.7	26.5±5.9	24.1±5.6	24.6± 4.9
LVEF(%)	60.2±8.7	59.8±9.1	55.9±9.6	56.9±10.0

(Mean±S.D.) *:$p<0.05$

LVEDD:Left ventricular end-diastolic dimension
LVESD:Left ventricular end-systolic dimension
LVSF :Left ventricular shortening fraction
LVEF :Left ventricular ejection fraction

Discussion : This study comfirms that left ventricular functions are not impaierd by the addition of lumbar epidural anesthesia under light general anesthesia in young children.

References: 1. Anesthesiology 65:A426,1986
2. Br.J.Anaesth. 6:1441,1987

S324

TITLE: EFFECTS OF HALOTHANE, ENFLURANE, ISOFLURANE, AND SEVOFLURANE ON THE MONOSYNAPTIC SPINAL REFLEX RESPONSE OF NEONATAL RATS

AUTHORS: S. Tsutahara, M.D., H. Furumido, M.D., T. Yamamura, M.D., Ph.D., O. Kemmotsu, M.D., Ph.D., F.C.C.M.
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Introduction: The monosynaptic spinal reflex response (MSR) of neonatal rats elicited in the ventral root after stimulation of the ipsilateral dorsal root is considered to be mediated by non-NMDA class glutamate receptors because it is completely blocked in the presence of 6,7-dinitroquinoxaline-2,3-dion (DNQX). We studied depressant effects of halothane (H), enflurane (E), isoflurane (I), and sevoflurane (S) on the MSR amplitude as a function of concentration of the anesthetic comparing at MAC value of each anesthetic.

Methods: The spinal cord of a neonatal rat was rapidly removed, placed in a chamber and superfused with the artificial cerebrospinal fluid (ACSF) at a rate of 2.5 ml/min. The ACSF consisted of (in mM) NaCl 125, KCl 4, NaH_2PO_4 1.25, $MgSO_4$ 1.5, $CaCl_2$ 2, $NaHCO_3$ 26, glucose 10, equilibrated with 95% O_2-5% CO_2 to adjust the pH at 7.4, and warmed to temperature of 33-34°C. Anesthetic gas was delivered from a specific vaporizer and bubbled in the perfusate. Anesthetic concentrations were determined by a gaschromatograph.

Results: Either of the anesthetics depressed MSR amplitudes in a concentration dependant fashion. Concentration-response curves for MSR amplitudes were constructed (Figure) and the concentration producing a half-maximum response (EC50) were 0.56, 0.65, 0.97 and 1.18 mM for H, E, I and S. Administrations of neither picrotoxine (100 μM, GABA antagonist) nor strychnine (40 μM, glycine antagonist) reversed the depressed MSR.

Discussion: Results indicate that values of EC50 determined by MSR amplitude were much higher than MAC values, suggesting that clinical levels of anesthesia are associated with only partial impairment of glutamate-mediated synaptic transmission. Enhancement of GABA- or glycine-mediated inhibition does not seem to be involved in a depressant action of these anesthetics on MSR amplitudes.

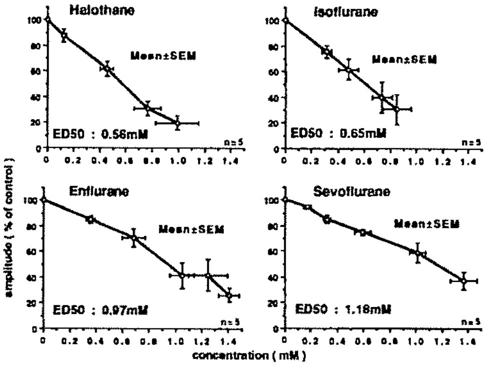

Fig. Concentration-response curves for H, E, I and S. Anesthetic concentrations in the bath were determined gaschromatographically.

S325

TITLE: A SURVEY INSTRUMENT TO ASSESS RESIDENT JOB SATISFACTION

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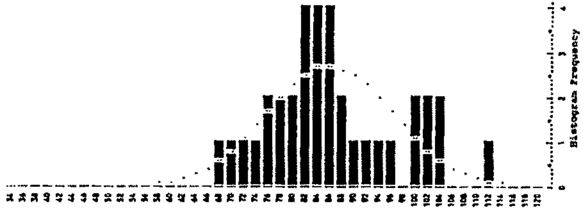
INTRODUCTION: To increase resident recruitment and retention, residency programs may strive to improve the resident work environment. Unlike the industrial workplace, however, the resident work environment has not been formally evaluated, and no instrument is available for this purpose. We developed an instrument to measure resident job satisfaction.

METHODS: Applying our knowledge of the relevant literature[1-3] and the residency training situation, we chose six factors to investigate: anesthesiologist faculty support, autonomy, education, interactions, work itself, and working conditions. A two-part survey instrument, including factor definitions, was prepared: 1) Paired comparisons were used to determine the relative importance of each factor; 2) Likert attitude scaling - Two positive and two negative attitude statements associated with each job factor were prepared. Responses of *strongly agree, agree, disagree, or strongly disagree* were assigned numeric values of 1 to 4. Each resident's score was the sum of the response values. An internal consistency check was performed and the Cronbach reliability coefficient was computed. Scatterplots and linear regression were used to assess the association of each question to the total attitude score. The questionnaire was presented to 35 CA-1 and CA-2 residents.

RESULTS: Education was the highest ranked factor, followed by anesthesiologist support, autonomy, interactions, work itself, and working conditions. The histogram of the Likert scores is shown below (higher numeric value=higher satisfaction). All questions had a positive correlation coefficient. The reliability coefficient alpha was 0.93.

DISCUSSION: Education was the most important factor affecting job satisfaction, and working conditions was the least important. The scores were normally distributed about a mean at the high end of the scale. Attitude scales must be formulated carefully to ensure that they are valid in both construct and content. The construct validity[4] of our instrument is indicated by the high index of internal consistency, evidence that a psychological construct is being measured. Careful attention to formulating attitude statements directly related to the job factors ensures content validity. An evaluation instrument of this type may be useful in improving resident satisfaction. Changes directed toward the factors judged more important by residents would minimize the cost-benefit ratio. Serial use of the instrument would help to assess the effectiveness of such changes.

REFERENCES:
1) AANA:49:43-51,1981
2) Medical Care:16:337-352,1978
3) Social Science and Medicine 12:195-212,1978
4) Measuring Social Attitudes, Mueller DJ, 1986



S326

Title: EFFECTS OF ACUTE VOLUME LOADING ON RIGHT VENTRICULAR FUNCTION AFTER CORONARY ARTERY SURGERY

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Intravascular volume expansion is commonly employed to generate preload recruitable stroke work (PRSW). However, ventricular dysfunction may limit generation of PRSW immediately after coronary artery surgery (CAS). The purpose of this study was to determine if the volumetric pulmonary artery catheter (PAC) provided additional useful information about fluid therapy beyond that obtainable with routine PAC monitoring after cardiac surgery.

After IRB approval, we studied 18 consenting adults within 24 h after elective CAS. Albumin (250 ml, 5% in NS) was administered IV over 5 min if wedge pressure (WP) was ≤ 15 mmHg (hemoglobin ≥ 8 gm/dl) and there was a clinical need to increase stroke volume. The fluid bolus was repeated if WP was < 18 mmHg or < preop WP. In addition to commonly monitored hemodynamic variables, right ventricular (RV) ejection fraction (EF) was measured at end exhalation with a rapid response thermodilution PAC. RV end diastolic volume (EDVI) and end systolic volume indices (ESVI) were calculated before and after each fluid bolus. Hemodynamic parameters were compared using ANOVA for repeated measures. Linear regression analysis was used to determine the relation between RV volumes, EF and other hemodynamic variables.

RVEF declined by 17% of the baseline value in 9 patients after volume loading (Group 1) and remained unchanged or increased in the remainder (Group 2). Overall, WP and RAP increased after fluid without intergroup differences. CI, SI and MAP increased progressively in both groups; CI and SI in Group 1 were less than Group 2 at all times. Before fluid, EDVI and ESVI were not different between groups; ESVI progressively increased in Group 1 but remained unchanged in Group 2. EDVI increased in both groups and was greater after the second fluid bolus in Group 1 compared to Group 2. No significant correlations were found between RAP or WP with SI, CI or EDVI. Baseline RVEF had significant correlations with the change in CI and EDVI ($r = .59$, $p = .009$ and $r = .72$, $p = .001$).

	GRP	BASELINE	BOLUS #1	BOLUS #2
SI ml/m²	1	24.8±4.8	26.7±5.3	27.8±5.1ʃ
	2	29.2±3.9*	31.2±5.3*	35.8±4.7*ʃ
RAP mmHg	1	10.8±2.1	12.0±1.9	13.4±2.6
	2	9.7±3.6	10.3±2.7	11.4±2.5
WP mmHg	1	13.1±1.9	14.1±1.4	16.0±1.7
	2	11.2±2.5	12.6±2.9	14.9±2.7
RVEF	1	36.6±4.7	34.8±4.7	30.2±6.2ʃ
	2	42.0±2.8*	42.7±3.7*	45.0±4.4*ʃ
RVEDVI ml/m²	1	68.5±14.4	77.1±16.1	92.9±14.3
	2	69.6±9.0	73.5±12.3	80.0±11.1*ʃ
RVESVI ml/m²	1	43.7±11.1	50.5±12.6	65.1±12.9ʃ
	2	40.4±6.1	42.3±8.3*	44.2±8.6*

*intergroup difference; ʃ difference from baseline; $p<0.05$

In cases where additional volume expansion resulted in significant declines in RVEF with increases in EDVI and ESVI after CAS, volumetric PAC data demonstrated decreases in preload recruitability of RV stroke work earlier than routine PAC data. Based on routine PAC data, additional fluid therapy could be justified in Group 1 patients, whereas volumetric PAC data indicated potentially deleterious effects on ventricular interdependence and function and the need for other means to increase stroke work. Volumetric PAC monitoring appears to be a useful guide for acute fluid therapy of patients recovering from CAS.

S327

Title: DOES A DIGITAL PRESSURE TECHNIQUE FOR INTERSCALENE BLOCK ALTER MEASURABLE SENSORY, MOTOR, OR DIAPHRAGM EFFECTS?

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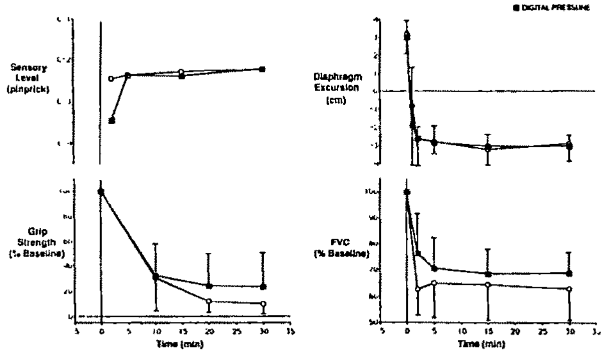
Introduction: Interscalene (IS) block provides reliable shoulder anesthesia by anesthetizing cervical nerve roots C3-C5. This is due to cephalad spread of local anesthetic to the cervical plexus from the interscalene brachial plexus injection point[1]. C3-C5 anesthesia leads to a reported 100% incidence of ipsilateral hemidiaphragm paresis[2] and sizeable diminutions in standard pulmonary function tests[3]. Winnie has advocated the use of digital pressure (DP) above injection site to inhibit cephalad spread of anesthetic solution[4]. This is supported by radiographic studies[4] but no clinical effects of DP have been published. Further, we have observed vagal effects including severe bradycardia provoked by digital pressure. Does DP alter cephalad sensory level or attenuate quantitative changes in motor function, diaphragm paresis, or pulmonary function that normally result from I.S. block?

Methods: IRB approval and written informed consent were obtained. 20 consecutive healthy patients were prospectively studied after random assignment to receive I.S. block (45ml 1.5% mepivicaine with 5 µg/ml epinephrine) with or without DP. Firm DP immediately above the injection site was held throughout injection and for an additional 60 seconds. The following were measured in supine position immediately before and at 2, 5, 15 and 30 minutes after I.S. block: 1) Sensory anesthesia by pinprick 2) Diaphragm excursion by ultrasonography 3) Forced vital capacity (FVC) and forced expiratory volume at 1 sec (FEV1) by computerized spirometry (Cybermedic). Hand grip strength by digital dynamometer (Asimow) was assessed at baseline and at 10, 20, and 30 minutes after injection.

Results: No clinical differences between groups in quality or duration of block for shoulder surgery were subjectively observed. The figure below shows mean sensory level, hand grip strength, diaphragm excursion, and FVC reduction as functions of time from injection. While there was an expected slower onset of high cervical sensory anesthesia with DP, there was no discernable difference by 5 minutes after injection. All 20 patients developed diaphragm paresis with no significant difference in onset or degree. Diminutions in FVC, FEV1, hand grip strength, or ability to lift arm or flex elbow against gravity did not differ significantly between groups.

Conclusions: DP during I.S. block did not significantly influence cephalad sensory anesthesia, motor anesthesia, or diaphragm paresis in this study. Whereas all 20 patients had adequate anesthesia for shoulder surgery, we did not evaluate the effects of DP on quality of anesthesia for more distal procedures where it may exert a positive effect.

References:
1. Anesth. & Analg. 58: 225-234, 1979.
2. Anesth. & Analg. 72: 498-503, 1991.
3. Regional Anesthesia. 15, No. 1S: 17, 1990.
4. Plexus Anesthesia. Saunders, 183-185, 1990.



S328

Title: Effect of Intraoperative Ketorolac on Postoperative Recovery Room Comfort

Authors: Valdrighi, JB, M.D., Behrman, KH, R.N., Disbrow, EA, M.A., Hanowell, LH, M.D.
Affiliation: University of California at Davis, Department of Anesthesiology, Sacramento, CA.

Introduction: Previous studies have demonstrated the equivalence of intramuscular ketorolac to morphine for treatment of postoperative pain.[1,2] In this study the effect of intraoperative administration of ketorolac on patient comfort during the immediate postoperative period was evaluated.

Methods: After human subject research committee approval and informed consent, patients undergoing general anesthesia for orthopedic limb or lower abdominal procedures were randomized to receive ketorolac or placebo. A double blind design was maintained throughout the study period. Upon surgical closure, either intramuscular ketorolac 60 mg or intramuscular placebo (saline) was administered. Efficacy of analgesia was evaluated using a visual analog pain score (VAS), postoperative morphine requirement, and time from recovery room admission to first requested morphine dose. Data is expressed as mean value ± standard error.

Results: Ten demographically similar patients were identified. The placebo group first requested analgesia 14 ±6 minutes after recovery room admission compared to 100 ±19 minutes for the ketorolac group ($p<.05$).

Table 1. Ketorolac vs Placebo

	Ketorolac	Placebo
First Narcotic(min)	100±19	14±6
Postop Morphine(mg)	1.2±1.2	10.6±3.6
Pain Score (VAS)	35±8.8	56.4±12.0
Postop Shivering	0 of 5	3 of 5

Discussion: Previous studies have not addressed intraoperative intramuscular administration of ketorolac. We document an improvement in postoperative analgesia after intraoperative intramuscular ketorolac. Larger patient sampling will be required to assess for differences between groups with respect to the other study variables.

References:
1. O'Hara. Clin Pharm Ther, 41:556-61, 1987.
2. Yee. Pharmacotherapy, 6:253-61, 1986.

S329

Title: COMPARISON BETWEEN 1 AND 2 % PROPOFOL EMULSION IN NEUROSURGICAL PATIENTS

Authors: R. Van Bos, MD, J. Van Hemelrijck, MD, B. Hulsey, MD, H. Van Aken, MD, PhD
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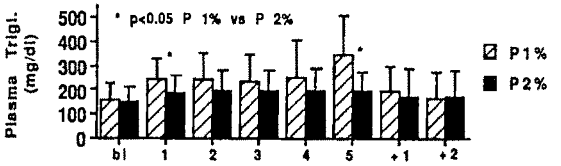
Introduction: Doubling the concentration of propofol (P) reduces the volume necessary for maintenance of anesthesia by 50 %. The aim of this IRB-approved, randomized, non-blinded study was to compare the pharmacodynamic effects, and the triglyceride (Tri) and cholesterol (Chol) plasma profiles, during anesthesia with respectively 1 % and 2 % P, in an identical lipid emulsion.

Methods: Following premedication with phenobarbital, 100 mg im, 56 consenting craniotomy patients (18-60 years of age, ASA class.1-2) were anesthetized with P, 1 or 2 %. All patients received A, 1 mg iv, immediately before induction. Anesthesia was induced with a P loading infusion at an infusion rate (IR) of 333 µg/kg/min. After 10 min, the P IR was decreased to 133 µg/kg for another 20 min, and, subsequently, to 100 µg/kg/min until skin closure. When the patients became unresponsive, pancuronium, 0.1 mg/kg iv, was administered and manual ventilation started. After the loading infusion (10 min) the patients were intubated, and mechanically ventilated with 40 % O_2 in nitrogen, maintaining end-tidal pCO_2 at 30 mmHg. Following intubation, an A infusion was started and titrated to maintain normotension. Results are expressed as mean values ± S.D. Anova, Chi-square, and paired t-tests were used for data analysis; $p \leq .05$ was considered significant.

Results: Both groups were identical concerning age, weight, type of procedures, and sex distribution. The hemodynamic profiles during the first 10 min of P infusion, induction time and dose, emergence time, total dose of P and A, were identical. The lower total infusion volume with P 2 %, resulted in a smaller increase in Tri concentrations. An identical decrease in Chol, was observed in both groups. Postoperative liver and renal function was normal in all patients.

Discussion: A 2 % emulsion formulation of propofol appears to have identical pharmacodynamic properties as Diprivan®, while the smaller volume of emulsion produces a smaller increase in plasma triglyceride concentration.

*** p < 0.001	P 1 %	P 2 %
induction time (sec)	166±56	185±75
induction dose (mg/kg)	1.02±0.4	1.2±0.6
anesthesia time (min)	245±51	262±58
tot.propofol IR (µg/kg/min)	116±7	115±10
propofol total volume (ml)	199±63	109±32***
alfentanil dose (µg/kg/min)	1.1±0.3	1.0±0.3
emergence (min)	29±22	30±13



(baseline, after 1 to 5 hours of infusion, 1 and 2 hours after discontinuation of P)

S330

Title: **MINIMAL EFFECTIVE CONCENTRATION OF ALFENTANIL FOR POSTOPERATIVE PAIN RELIEF**

Authors: MCO van den Nieuwenhuyzen, MD, FHM Engbers, MD, HJM Lemmens, MD, AGL Burm, PhD, AA Vletter, BSc, JW van Kleef, MD, JG Bovill, MD
Affiliation: Department of Anesthesiology, University Hospital Leiden, Leiden, The Netherlands

Introduction: Alfentanil (Alf) can provide effective postoperative analgesia[1] but the Minimum Effective Concentration (MEC) for analgesia has not been determined. We examined the variation in MEC between patients and with time after orthopedic surgery.

Methods: With institutional approval and informed consent, 20 patients ASA I-II, 21-65 yrs, were studied after orthopedic surgery. Premedication was with temazepam, 20-30 mg. Anesthesia was induced and maintained with $N_2O:O_2$ (2:1) and a computer controlled infusion of Alf (CCIA). CCIA was stopped 20 min before the end of surgery. Postoperatively, when patients reported pain CCIA was restarted with as target concentration the plasma concentrations (C_p) calculated by the computer at that time. Every 15 min the target C_p was increased or decreased by 5 or 10 ng/mL, according to the patient's response. Arterial blood samples, for determination of plasma Alf concentration were taken before and 15 min after every change in target C_p. MEC was defined as the measured Alf concentration at which the patient was oriented, with a VAS score < 3, and indicated no need for additional analgesia. Individual MECs were determined at the start of the study, at 9 pm on the day of surgery, and at 9 am and 9 pm the next day. Respiration rate (RR) and oxygen saturation (SaO_2) were continuously monitored. Pain scores, level of sedation and side effects were recorded. A sigmoid maximum effect model was fitted to the percentage of patients with a '$C_p \geq$ MEC' versus C_p (E_{max}=100%). The effect of time on MEC was determined by the Friedman test. P<0.05 was regarded significant.

Results: All patients were satisfied with the analgesic therapy. The number of patients with Alf C_p < 1 ng/mL at the 4 study times was 0, 0, 2, 6. In the remaining patients MEC did not change with time. C_p50, the plasma concentration above which 50% of the patients had effective analgesia ($C_p \geq$ MEC), was 58, 49, 60 and 55 ng/mL at the 4 study times. The percentage of patients with a $C_p \geq$ MEC vs C_p at 9 pm on the day of surgery are shown in figure 1. Frequently noted side effects were nausea, vomiting and urinary retention. Respiratory depression (RR < 10 or SaO_2 < 90%) did not occur.

Discussion: This study showed that intersubject variability in MEC is substantial, whereas individual MEC values are relatively stable during the period when analgesia is required.

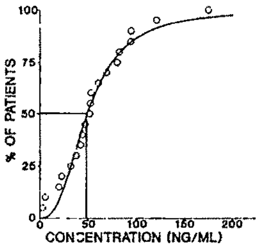


Figure 1. Percentage of patients with $C_p \geq$ MEC vs C_p and fitted curve.

Reference: 1. J Pain Symptom Manag, 5, 249-258, 1990.

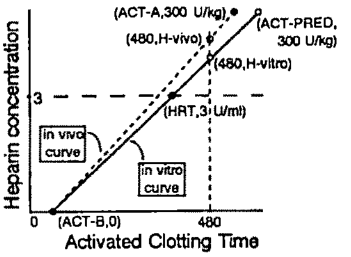
S331

AN IN VITRO TEST TO PREDICT HEPARIN RESPONSE

D Van Riper MD, J Horrow MD, F LaDuca PhD*, D Nyhan MD**, C Pan PhD* [Depts of Anesth., Hahnemann Univ. Phila. PA, and **Johns Hopkins Univ. Baltimore MD, and *ITC, Edison, NJ]

Patients receive heparin for cardiopulmonary bypass (CPB) without regard to drug potency or patient response variabilities.[1] We evaluated an assay aimed at optimizing heparin dose. The heparin response test (HRT) consists of an ACT tube to which has been added lyophilized heparin matched in potency and lot to the heparin which the patient will receive (final [heparin] =3 U/ml).

METHODS: With IRB approval, 191 patients for CPB at 2 institutions enrolled. No patient received heparin within 3 hr of testing. Calibrated Hemochron® machines performed all ACTs in duplicate. Assuming no initial heparin and a linear heparin dose–ACT response relationship, we constructed in vitro and in vivo curves: The in vitro curve used baseline ACT (ACT-B) and the HRT time (fig.). This curve permits estimation of the amount of heparin to achieve a target ACT=480 (H-vitro) and the ACT expected from giving the patient 300 U/kg (ACT-PRED). Patients then received 300 U/kg of heparin. Five minutes later, an ACT (ACT–A) was measured. Using weight and height to estimate plasma volume, we constructed an in vivo curve (fig.) which allows determination of H-vivo, the amount of heparin required to yield an ACT of 480 s. Regression analysis determined relationships of HRT to H-vivo and ACT–A to ACT–PRED. P<.05 was significant.



RESULTS: 300 U/kg heparin produced a measured ACT–A of 573±210[SD] s (N=191), yielding 287±101 U/kg (H-vivo) for ACT 480. H–vivo mean±SD separated patients into 3 groups: resistant (R) to heparin (H–vivo >287+101); sensitive (S) (H–vivo <287–101); and those remaining (MID). The table, displaying aggregate data, demonstrates that the heparin dose predicted by HRT (H-vitro) follows the actual in vivo results. The in vitro test correlated well with in vivo data for ACT (r=0.88, N=191, P<0.05) and heparin dose to achieve an ACT of 480 (r=0.70, N=191, P<0.05).

TABLE. Results of in vitro testing segregated by in vivo response.

Group	N	H–vivo	HRT *	H–vitro **
R	32	>388 U/kg	323±30 s	406±75 U/kg
MID	135	186–388	408±64 s	267±50 U/kg
S	24	<186 U/kg	612±95 s	147±34 U/kg

Newman-Kuels Test (P<0.05): *R<MID<S ** R>MID>S

DISCUSSION: Drug potency variation and pharmacokinetic and pharmacodynamic variability confound achievement of precise anticoagulation with heparin. HRT accounts for both drug potency variation and pharmacodynamic variability; further discrepancies arise from pharmacokinetic variation. The HRT requires two significant assumptions: (1) a linear heparin dose–ACT response relationship; (2) predictable pharmacokinetics and blood volume from height and weight. Despite these limitations, HRT predicts well patient heparin response. Additional studies may determine whether its use to tailor heparin dose provides clinical benefit.

REFERENCE: 1. J Thorac Cardiovasc Surg 69:674, 1975

S332

Title: THE REDUCTION IN UPPER ESOPHAGEAL SPHINCTER PRESSURE WITH THIOPENTAL

Authors: RG Vanner FCAnaes, BJ Pryle FCAnaes, JP O'Dwyer FCAnaes, F Reynolds MD FCAnaes.
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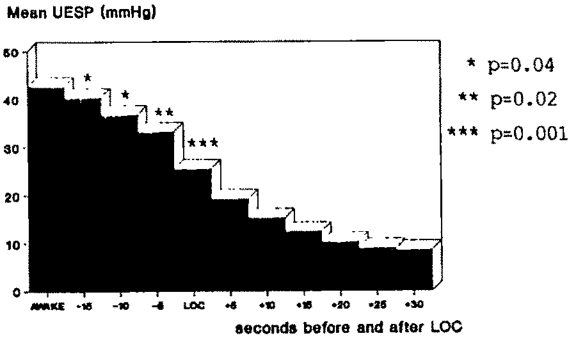
Introduction: The upper esophageal sphincter is formed mainly by cricopharyngeus, a striated muscle whose tone creates a sphincter pressure which prevents the regurgitation of esophageal contents into the pharynx. The neuromuscular blocking drug succinylcholine usually causes an abrupt fall of upper esophageal sphincter pressure (UESP) with the onset of fasciculations(1). In those patients at risk of regurgitation cricoid pressure is designed to counteract this reduction in UESP, but there is controversy about whether it should be applied before or after loss of consciousness (LOC). Mean UESP is 40 mmHg when awake and falls to 8 mmHg during deep sleep(2). Although intravenous pentobarbital decreases UESP in dogs(3) the effects of anesthetic drugs have not been previously studied in humans. We have recorded UESP during LOC with a rapid intravenous injection of thiopental. UESP was measured continuously by a 4.0mm diameter water perfused manometry catheter with a 6cm sleeve device(4).

Method: After informed consent, 16 patients (9 female), ASA I and II, were premedicated prior to elective surgery with intramuscular papaveretum (mean dose 0.19 mg/kg) with hyoscine. After the catheter was zeroed at the cricoid cartilage, it was swallowed via the anesthetized nose, and positioned so that the sleeve straddled the sphincter and faced posteriorly. The patient was pre-oxygenated while lying on a standard pillow and the baseline awake UESP was recorded two minutes later. UESP was recorded continuously by a printer as thiopental 4.0mg/kg was injected into a large forearm vein over four seconds and flushed with saline. LOC was timed to loss of eyelash reflex. UESP was also noted one minute after succinylcholine 1.0 mg/kg. The paired t-test was used to assess the significance of a decrease in UESP from the awake value.



Results: Mean age was 46(range 33-56) years. Mean time to LOC was 20(range 16-29) seconds. UESP was (mean±SD): awake, 43±19 mmHg; at LOC, 26±13 mmHg; 30 seconds after LOC, 9±7 mmHg; after succinylcholine, 8±5 mmHg. The figure shows that mean UESP started to decrease before LOC and the most rapid fall was in the five seconds before LOC. UESP after succinylcholine was not significantly different from that after thiopental (p=0.4). Only one patient, who was drowsy following premedication, had an unusually low awake UESP of 8.0 mmHg.

Discussion: Thiopental causes a rapid fall in UESP which usually starts before LOC. To counteract this fall in UESP, in patients at risk of regurgitation, cricoid pressure should therefore be applied before LOC, as Sellick originally described(5). Heavy premedication may reduce UESP in some patients.

References:
1. British Journal of Anaesthesia 1963; 35: 219-223.
2. Gastroenterology 1987; 92: 466-471.
3. American Journal of Physiology 1990; 259: G245-251.
4. Digestive Diseases and Sciences 1987; 32: 121-128.
5. Lancet 1961; i: 404-406.

S333

TITLE: IS INTRAVENOUS KETOROLAC SAFE IN CRITICALLY ILL PATIENTS?

AUTHORS: H Vega MD, R McGory PharmD, KJ Schwenzer MD

AFFILIATION: Department of Anesthesiology University of Virginia HSC, Charlottesville, Virginia

INTRODUCTION: Ketorolac tromethamine (KT) is the first parenteral nonsteroidal antiinflammatory drug approved for use in the U. S. The intravenous route may be preferable in the critically ill secondary to decreased muscle mass and regional absorptive changes. Following anecdotal institutional reports of hypotension after rapid IV administration, we undertook this study to measure the safety of KT in the critically ill patient population.

METHODS: Following institutional approval, 8 ICU patients received 30 mg of KT IV over 30 seconds. Patients were hemodynamically stable prior to being entered into the study. Vasopressor therapy was limited to renal dose dopamine. All narcotics were held for 2 hours prior to KT administration. Patients with serum creatinine > 2.0 (normal 0.7 - 1.3 mg/dl), or ongoing clinical or laboratory proven coagulopathy were excluded. Measured parameters included systolic diastolic, and mean BP, HR, CVP, and/or PAD immediately prior to injection and then at 2, 4, 6, 8, 10, 15, 20, 25, 30, and 35 minutes.

RESULTS: Hemodynamic parameters post injection of KT varied no more than 10% from prestudy values. There was no sensation of burning on injection, nor other untoward effects.

DISCUSSION: KT is potentially beneficial in the critically ill secondary to its analgesic capabilities and lack of respiratory depression (1, 2). Rapid IV administration of KT had no adverse hemodynamic effects in this select group of patients.

1. Rubin P et al. Ketorolac tromethamine analgesia: no post-operative respiratory depression and less constipation. Clin Pharmacol Ther 1987; 41:182

2. Brandon Bravo LJC et al. The effects on ventilation of ketorolac in comparison with morphine. Eur J Clin Pharmacol 1988; 35:491.

S334

TITLE: A COMPARISON OF MIDAZOLAM AND DIAZEPAM AS ORAL PEDIATRIC ANESTHETIC PREMEDICANTS

AUTHORS: T.R. VETTER, M.D.

AFFILIATION: DEPT OF ANESTHESIOLOGY, CHILDREN'S HOSP MED CENTER OF AKRON, AKRON, OH 44308

INTRODUCTION: Midazolam is reported to be more effective than placebo as an oral pediatric premedicant (1). Routine such use of midazolam at our hospital would result in an additional $185,000/yr in pharmacy charges (6,000 outpatients) and would require additional nursing staff and appropriately equipped bed space. Therefore, the present, similarly designed study was undertaken to validate the above authors' conclusions; to determine if less expensive diazepam (with a $0.10/mg vs. $2/mg charge) is a viable alternate oral pediatric premedicant; and to assess the respiratory effects of both benzodiazepines.

METHODS: After IRB protocol approval and with informed parental consent, 90 patients between the ages of 1 and 10 yrs were randomly assigned to one of three premedicant groups. In a double-blinded manner, either a placebo (P), 0.6 mg/kg of midazolam (M), or 0.3 mg/kg of diazepam (D) was administered orally, no less than 20 mins prior to surgery. The child's reaction to parental separation was then assessed with a 3-point behavioral scale: 1=excellent (calm, drowsy); 2=good (anxious but easily reassured); 3=poor (anxious, tearful, combative). Once in the OR, an initial room air SaO_2 was obtained via pulse oximetry. Prior to IV placement, each child then received 70% N_2O in 30% O_2 via a flavored mask. The child's initial acceptance of this mask was scored on a 4-point scale: 1=excellent (unafraid, cooperative, accepts mask readily); 2=good (slight fear of mask, but easily calmed); 3=fair (moderate fear of the mask, not easily calmed); 4=poor (afraid, combative, crying). Lastly, each patient's length of stay in the PACU (mins) was recorded. Statistical analysis involved ANOVA for continuous data and the Kruskal-Wallis test for nonparametric data. A $p < 0.05$ was considered significant with all tests.

RESULTS: The three study groups were similar in age and premedication times. No population differences in initial SaO_2, parental separation scores, mask acceptance scores or PACU length of stay were demonstrated among P, M and D (Table 1).

DISCUSSION: The present study failed to confirm the previously reported superiority of a similar dose of midazolam over placebo as a pediatric anesthetic premedicant (1). Likewise, diazepam does not appear any more effective than placebo. A given child's preoperative anxiety and lack of cooperation can certainly result in stress for the patient, parent and medical staff. However, as witnessed here, not all children outwardly react to the surgical experience in negative ways. Rather than implementing the routine use of a sedative, the management challenge appears to be the selective identification of those children at risk for an acute negative reaction and hence psychological trauma. As used here, neither benzodiazepine appears to cause respiratory depression.

REFERENCES: 1) Anesthesiology 73(5): 831-34, 1990.

Group (N)	Initial RA SaO_2 (%)	PACU (mins)	Separation Score (1/2/3)	Mask Score (1/2/3/4)
P (30)	99 ± 1.1	77 ± 12	19/6/5	18/2/4/6
M (30)	98 ± 1.5	86 ± 21	25/5/0	22/6/1/1
D (30)	99 ± 1.2	80 ± 16	21/6/3	19/7/3/1

Table 1. Summary of effects of P, M, and D on SaO_2 and PACU stay (mean ± SD); and parental separation and mask acceptance scores (# of patients with each score). No significant differences noted.

S335

TITLE: AN ALTERNATE METHOD FOR PEDIATRIC ANESTHETIC INDUCTION

AUTHORS: T.R. VETTER, M.D., W.G. ELLIS, M.D.
AFFILIATION: DEPT OF ANESTHESIOLOGY, CHILDREN'S HOSP MED CENTER OF AKRON, AKRON, OH 44308

INTRODUCTION: Prior to venous cannulation and intubation, airway and cardiovascular compromise can occur during pediatric halothane inhalation inductions. Such events are a leading cause of closed pediatric malpractice claims (1). Nitrous oxide has been shown in children to be safe and effective in reducing the pain and anxiety associated with preoperative venous cannulation (2). We assessed the safety of an alternate intravenous method for pediatric anesthetic induction that is relies on such use of N_2O.

METHODS: With IRB approval, quality assurance data were prospectively collected on 2002 consecutive ASA I-III pts, ages 1 mo to 16 yrs, anesthetized between 1/91 and 6/91. All had been fasted; 433 had received 0.02 mg/kg po of atropine as a preoperative antisialogue. All received 70% N_2O in O_2 via a flavored mask for 1-3 mins prior to venous cannulation. Then on 100% O_2, all underwent an intravenous induction with pentothal and either atracurium or succinylcholine. Isoflurane (1-2%) was administered prior to intubation. Critical induction events noted included: excitement (stage 2), coughing, vomiting, airway obstruction, laryngospasm, bradycardia, hypotension and hypoxemia ($SaO_2<90\%$). Chi-square analysis ($p<0.05$ considered significant) was used to assess any effect of oral atropine on the frequency of airway obstruction, laryngospasm and bradycardia.

RESULTS: Demographic and induction critical incidence data are summarized in Table 1. When given as an oral premedicant, atropine had no significant effect in this population on the frequency of airway obstruction, laryngospasm and bradycardia.

DISCUSSION: Pediatric inductions in the US routinely involve the mask administration of a progressively increasing concentration of halothane so as to obtain a rather deep anesthetic plane prior to venous cannulation (3); such inductions can result in airway and cardiovascular compromise, particularly in the infant and younger child. Moreover, this conventional method can be especially challenging for the solo or relatively inexperienced anesthesiologist (4). The alternate induction method presented here appears to be both safe and more applicable under diverse clinical circumstances than a conventional halothane induction.

REFERENCES:
1) Anesthesiology 71: A1174, 1989.
2) Anesthesiology 72: 269-71, 1990.
3) Smith's Anesthesia for Infants and Children: 265-67, 1990.
4) Anesthesiology 73: A1045, 1990.

Age in Years	< 1	1 - 3	4 - 8	9 - 16	Total
N	244	651	701	409	2002
Excitement	0.8	0.7	0.7	0	0.6
Coughing	1	0.6	1	0.5	0.9
Vomiting	0	0	0.6	0.2	0.2
Obstruction	0	0.6	0	0	0.2
Laryngospasm	0	0	0	0	0
Bradycardia	0	0	0	0	0
Hypotension	0	0	0	0	0
Hypoxemia	0	0.2	0	0	0.05

Table 1. Patient Age Profile and Induction Critical Incidents Data (reported as percentages of N)

S336

Title: The 40 Hz Auditory Steady-State Response for Monitoring the Level of Consciousness

Authors: C. Villemure; G. Plourde; O. Castillo

Affiliation: Departments of Anaesthesia, McGill University and Royal Victoria Hospital, Montreal (Quebec) CANADA

Introduction: The 40 Hz auditory steady-state evoked response (ASSR) is markedly attenuated or abolished during unconsciousness induced by thiopental, sufentanil or isoflurane [1,2]. If the attenuation of the ASSR does indeed reflect unconsciousness, one predicts that 1) the changes of the ASSR will not be dose-dependent provided that consciousness is absent and 2) during emergence from anesthesia, reappearance of the ASSR will coincide with the return of consciousness. We have verified this during enflurane-N_2O anesthesia.

Methods: After institutional approval and informed consent, 12 unpremedicated women (aged 18-50) undergoing breast reduction were tested. Fentanyl (3 $\mu g.kg^{-1}$) and thiopental (3-5 $mg.kg^{-1}$) were used for induction and vecuronium for tracheal intubation. Anesthesia was maintained with N_2O (66% end-tidal, ET) and enflurane (0.5, 0.8 or 1.1% ET, 4 patients per concentration, random assignment). Neostigmine and glycopyrrolate were given 10 min before the end of surgery.

The ASSR was recorded before induction (control), after fentanyl (before thiopental) during surgery (after $\geq$ 15 min at desired concentration), emergence (a 5 min period after opening of the eyes on command) and recovery (40 min after emergence). We also recorded before emergence, as soon as the ET concentration of enflurane and N_2O were $\leq$ 0.3% and $\leq$ 30% and until the patients opened their eyes on command, moved or coughed.

Stimuli consisted of 500 Hz tonebursts (15 ms, 90 dB peSPL) presented binaurally via insert earphones at a rate of $40.sec^{-1}$. The EEG was recorded from Cz referenced to right mastoid (0.3-100 Hz, sampling rate 287.4 Hz, 3,564 ms epoch). Epochs were averaged by groups of 80-100. Amplitude and phase at 40 Hz were obtained by Fast Fourier Transform (FFT). ANOVAs for repeated measures and Tukey's HSD tests were used for analysis. The Rayleigh test for phase coherence was used to determine if the ASSR could be distinguished from noise [1]. Criterion for significance was $p < 0.01$.

Results: The amplitude of the ASSR during surgery was much smaller than during all other periods ($p < 0.01$) (Table). There were no other significant differences. The changes of the ASSR were similar for the 3 enflurane concentrations. Phase coherence was present however during all periods indicating that the ASSR persists during surgery despite the drastic amplitude reduction. We were able to record before emergence in only 5 patients and the ASSR was as small as during surgery. The other patients coughed or moved too soon for recording.

Discussion: The ASSR is drastically attenuated (but not abolished) during enflurane-N_2O anesthesia. The attenuation is not dose-dependent and appears to reflect unconsciousness.

References:
1. Plourde G, Picton TW. Anesth Analg 71:460-8, 1990.
2. Plourde G, Boylan JF. Br J Anaesth 66:683-91, 1991.

ASSR Amplitude (μV)
Mean (SD)

	CONTROL	FENTANYL	SURGERY	EMERGENCE	RECOVERY
Enflurane 0.5%; N=4	0.27 (0.02)	0.27 (0.09)	0.03 (0.01)	0.29 (0.22)	0.21 (0.08)
Enflurane 0.8%; N=4	0.27 (0.11)	0.34 (0.24)	0.02 (0.01)	0.14 (0.09)	0.25 (0.16)
Enflurane 1.1%; N=4	0.27 (0.08)	0.35 (0.06)	0.05 (0.02)	0.15 (0.07)	0.34 (0.15)
All Groups N=12	0.27 (0.07)	0.32 (0.15)	0.03 (0.02)	0.19 (0.14)	0.27 (0.13)

S337

Title: POWER AND SAMPLE SIZE CALCULATIONS IN CLINICAL TRIALS FROM ANESTHESIA JOURNALS

Authors: E Villeneuve, M.D, A Mathieu, M.D., CH Goldsmith, Ph.D.
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Introduction: In a trial where no statistically significant effect can be detected, power and sample size (P/SS) are crucial methodological considerations.[1] Low P/SS can lead to a false negative result and dismissal of a potentially beneficial intervention. We report the extent to which P/SS, and parameters essential for such calculations are present in controlled clinical trials (CCT), with $n \leq 10$/ group, from the anesthesia literature.

Methods: Having identified all the CCT in humans from the 1989 issues of Anesth Analg, Anesthesiology, Br J Anaesth, Can Anaesth Soc J and Ann Fr Anesth, we randomly selected 20 from each journal in order to achieve 90% power to detect a 20% difference in scores between journals. These 100 articles were randomly allocated to, and read in random order by 2 authors. P/SS was one of 10 methodological criteria judged to be present (1) or absent (0). In CCT with an $n \leq 10$/group, additional parameters necessary to calculate P/SS were also recorded: 1) clinically important level of change in primary outcome, 2) type I error, 3) naturally occurring variance, and 4) type II error or sample size. Primary outcome was defined as the measurement upon which the conclusion of the study was based. Clinical importance referred to the minimum amount of change deemed clinically relevant by the authors of the article. When the latter failed to identify a primary outcome or the level of a clinically important change, P/SS calculations were based on the outcome's result showing the largest difference between groups.[2] Studies with both statistically significant and non-significant outcomes were classified as equivocal rather than negative or positive.

Results: 36 CCT (84% randomized) had an $n \leq 10$/ group, none of which reported P/SS calculations. As seen in the table, less than 1/3 of positive studies fell in the $n \leq 10$, whereas close to 60% of equivocal or negative studies had a very small n. Also revealing is the fact that only 5 out of these 21 negative and equivocal studies for which power could be calculated have values $\geq 75\%$. Type II error and clinical importance were omitted in most CCT and P/SS in all but 2 out of 100.

Discussion: As shown in the table, studies with small sample sizes associated with low power values provide a lower probability of rejecting the null hypothesis and often lead to a negative or equivocal study conclusion. P/SS calculations are an essential part of any well planned CCT and their reporting should be required. This is especially true for negative studies and should help methodological assessment while reducing the risk of rejecting a potentially beneficial treatment.[3]

STUDY CONCLUSIONS, SAMPLE SIZE, CALCULATED POWER

Conclusion	Negative n=23	Equivocal n=20	Positive n=57
≤10/group	13 56%	12 60%	16 28%
No Articles & Power %	7/11 ≤10% 4/11 ≥75%	9/10 <50% 1/10 =75%	3/15 50% 12/15 >85%

References: 1.NEJM 299:690-694, 1978. 2.Biometrics 44:1157-1168, 1988. 3.Ann Intern Med 113:724-728, 1990.

S338

Title: EVALUATION OF PROPOFOL PHARMACOKINETIC DATA SETS BY COMPUTER SIMULATION

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Introduction: It is essential, when using computer controlled infusion (CCI) techniques, to incorporate the optimal pharmacokinetic data set. We investigated the performance of a CCI system when supplied with 5 different published propofol pharmacokinetic data sets.

Methods: With ethics committee approval and informed consent, 9 female patients, ASA 1, aged 20-50 yr, were studied. A radial artery was cannulated for blood sampling. Propofol was administered by a CCI pump, supplied with 3-compartment pharmacokinetic data[1]. The initial target blood concentration of 1 µg/ml was increased every 12 min by 1 µg/ml until patients lost consciousness. Arterial blood samples were obtained before and every 3 min during the study for analysis of blood propofol concentration. Infusion rate-time data, stored each min on computer disk, were then read by a simulation program that recalculated the predicted concentrations for each patient, using 4 other propofol pharmacokinetic data sets[2-5]. For each measured blood propofol concentration, 5 predicted concentrations were thus obtained. For each blood sample the performance error[6] of the 5 predicted concentrations was calculated as $((C_m-C_p)/C_p) \times 100$, where C_m and C_p are the measured and predicted concentrations. The bias and inaccuracy of each pharmacokinetic data set were then assessed by the median performance error (MDPE) and the median absolute performance error (MDAPE). When the 95% confidence interval of the bias included zero, it was concluded that no significant bias had occurred.

Results: The mean (± SD) age and weight of the patients studied were 36 ± 8 yr and 63 ± 10 kg. A total of 117 blood samples were analyzed. The 2 compartment pharmacokinetic data set of Shafer et al[2] showed no significant bias, whereas in all 3 compartment pharmacokinetic data sets[1,3-5] C_m exceeded C_p (table).

Discussion: We conclude that the Shafer pharmacokinetic data set is most appropriate for CCI techniques in young healthy females.

Table: The bias and inaccuracy (MDPE, MDAPE, 25th-75th perc) and 95% confidence bounds of the bias of 5 kinetic data sets.

Pharmacokinetic data set	MDPE (25-75%)	MDAPE (25-75%)	95% Confidence bounds of MDPE
Gepts[1]	26 (9-40)	27 (14-41)	19-32
Shafer[2]	4 (-9 - 15)	12 (5-22)	-2 - 7*
Kirkpatrick[3]	112 (88-134)	112 (88-134)	106-119
Cockshott[5]	22 (8-36)	23 (13-38)	18-29
Tackley[4]	27 (14-41)	29 (15-41)	24-34

* No significant bias.

References:
1: Gepts et al, Anesth Analg 66: 1256-63, 1987.
2: Shafer et al, Anesthesiology 69: 348-56, 1988.
3: Kirkpatrick et al, Br J Anaesth 60: 146-50, 1988.
4: Tackley et al, Br J Anaesth 62: 46-53, 1989.
5: Cockshott et al, Br J Anaesth 59: 941P, 1987.
6: Raemer et al, Anesthesiology 73: 66-72, 1990.

S339

Title: URAPIDIL: A SAFE AND EFFECTIVE DRUG FOR BLOOD PRESSURE CONTROL DURING AORTIC CROSS-CLAMPING

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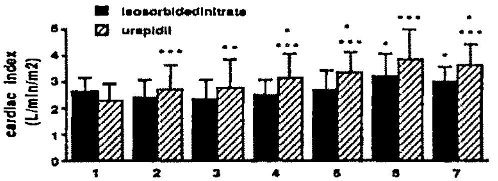
Introduction: Pharmacologic prevention of the circulatory consequences of aortic cross-clamping (AO-X) is mandatory during aortic surgery. The aim of the study was to compare the efficacy, safety, and hemodynamic profiles of pressure control with Urapidil (U), an α_1-adrenoceptor blocking agent with agonistic activiy at the central serotonin-receptors (preventing reflex tachycardia), or with Isosorbide dinitrate (I), our standard therapy.

Methods: With IRB-approval and informed consent, 36 male patients (ASA II-III) scheduled for abdominal aortic surgery were randomly assigned to receive either U or I. Anesthesia was induced with etomidate and alfentanil, and maintained with an alfentanil infusion and N_2O 66 %. Approximately 10 min before AO-X incremental 5 mg bolus doses of U, or a continuous infusion of I, was administered to obtain a mean arterial pressure (MAP) of 80 mmHg. During the AO-X period additional U or I was administered to maintain MAP between 90 and 110 mmHg. Before declamping (D) MAP was increased to 100-120 mmHg by discontinuing U or I and volume loading. Hypotension after D was treated with neosynephrine or ephedrine. Hemodynamic profiles were registered before and after study drug administration (times 1 and 2), 3 and 10 min following AO-X (times 3 and 4), before, 3 and 10 min following D (times 5, 6, and 7). Automatic ST-segment analysis of lead II and V_5 was used for the detection of myocardial ischemia. The oxygen extraction ratio (O_2-ER) at times 1, 4, 5 and 7 was determined. Paired t-test and Anova were used for statistical analysis, $p<0.05$ considered significant.

Results: Both groups were similar with respect to demographic profiles and peroperative alfentanil and fluid therapy. Heart rate, systemic, pulmonary arterial, and right and left atrial pressures were identical at all measurement times. In contrast to I, U produced a significant increase in cardiac index (CI) (Figure) before and during AO-X, as a result of a significant decrease in systemic vascular resistance and increase in stroke volume index. As a consequence the O_2-ER decreased significantly following U. Vasopressor support following D was needed in 3 and 5 patients after I and U respectively. ST-depression of 1 mV or more was noted more frequently in patients receiving I (28 %) than in patients receiving U (17 %).

Discussion: Urapidil appears to be an effective and safe alternative to isosorbide dinitrate for the prevention of the hemodynamic consequences of aortic cross-clamping, with the advantage of improving CI.



* p < 0.05 difference between Groups
* p < 0.05, ** p ≤ 0.01, *** p ≤ 0.001 compared to baseline

S340

Title: VENTILATION AND BODY TEMPERATURES DURING LAPAROSCOPIC VS. OPEN CHOLECYSTECTOMY

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Introduction: Laparoscopic cholecystectomy has quickly emerged as a less invasive alternative to open cholecystectomy. During short gynaecological procedures, peritoneal insufflation of carbon dioxide has been observed to change respiratory acid base balance (1). Our hypothesis was, that body temperatures and ventilatory requirements do not differ during cholecystectomies performed either through laparoscope or laparotomy.

Methods: Twenty consecutive consenting female patients (ASA I-II) scheduled for laparoscopic (LCC, n=10) or open (OCC, n=10) elective cholecystectomies were studied. Anesthesia was induced with thiopental and fentanyl, maintained with enflurane (end-tidal 0.6%) in 30%/70% oxygen/nitrous oxide and vecuronium. Tidal volume was set to 10 ml/kg and end tidal carbon dioxide kept at 5.5 % by adjusting the ventilatory rate (RR). Expiratory minute ventilation (MV) was determined with a spirometer. Intravenous infusions and surgical drapings were standardized. Body temperatures were measured in the lower third of the oesophagus (Toes), rectum (Trec) and on the big toe (Ttoe) as well as room temperatures. The hypotheses were tested using Student's t-test and two-way analysis of variance, taking P<0.01 as a limit of significance.

Results: Demographic patient data, the operation durations (LCC 88±28 min, OCC 71±17 min) and room temperatures did not differ between the two groups.

Table 1. Ventilatory data (mean ± SD).

		MV (l/min)	RR (breaths/min)
Control	LCC	4.0 ± 0.8	7.1 ± 1.4
	OCC	4.1 ± 0.8	6.8 ± 0.8
30 min	LCC	7.1 ± 4.4 \	12.5 ± 4.0 \
	OCC	4.4 ± 0.8 /*	6.9 ± 1.0 /*
60 min	LCC	6.5 ± 0.9 \	11.4 ± 2.9 \
	OCC	4.4 ± 1.0 /*	6.9 ± 1.1 /*

* significant

Table 2. Temperatures (°C ,mean ±SD).

		Toes	Trec	Ttoe
Control	LCC	37.1 ± 0.5	37.2 ± 0.4	31.1 ± 4.2
	OCC	36.9 ± 0.4	37.1 ± 0.3	31.2 ± 3.1
30 min	LCC	36.5 ± 0.5	36.8 ± 0.4	34.9 ± 1.6
	OCC	36.3 ± 0.5	36.7 ± 0.4	34.8 ± 0.8
60 min	LCC	36.4 ± 0.4	36.7 ± 0.4	34.7 ± 0.8
	OCC	36.3 ± 0.3	36.6 ± 0.3	34.7 ± 0.8
End of	LCC	36.3 ± 0.4	36.6 ± 0.4	34.4 ± 1.8
surgery	OCC	36.2 ± 0.5	36.5 ± 0.4	34.1 ± 1.2

Discussion: LCC required significantly larger minute ventilations than OCC for maintenance of respiratory homeostasis. Body temperature changes were similar and moderate in both groups. The large MV during LCC may have accounted for the heat loss comparable to that caused by open abdominal cavity. Albeit being less invasive surgically, minimal access procedures require equally comprehensive gas monitoring and anesthetic management as traditional laparotomies.

References: Anaesthesia 25:382-390, 1970.

S341

Title: DO WE HAVE A WAY TO MEASURE THE ADEQUACY OF HEPARINIZATION DURING CARDIOPULMONARY BYPASS?

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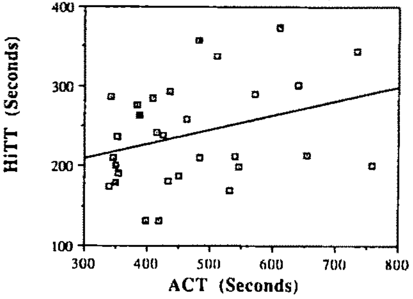
Introduction: In patients requiring cardiopulmonary bypass (CPB), the activated clotting time (ACT) is often used for determining the adequacy of heparinization and protamine neutralization. Distortion of the relationship between ACT and blood heparin concentration during CPB has led some physicians to recommend monitoring of the heparin concentration. We evaluated the coagulation properties of blood in CPB patients by using ACT, ACT with kaolin (HR-ACT), heparin level measurement (by protamine titration), and high-dose thrombin time (HiTT).

Methods: After obtaining approval from the IRB and informed consent from each patient, we investigated 27 patients requiring CPB (18 CABG, 5 valve replacements, and 4 congenital malformations). Heparin, 2 to 4 mg/kg, was administered IV before the cannulation of the aorta. After the end of CPB, protamine sulfate was given IV over 10 min in a dose of 1.0-1.5 mg/mg heparin. A whole-blood sample was obtained before and 5 min after heparinization, at 60 and 90 min of CPB, and 10 min after protamine injection. ACT and HiTT were measured by means of a Hemochron device. HR-ACT and heparin level were determined with the Hepcon® HMS system.

Results: The heparin concentration as measured with the Hepcon system did not match the heparin dose in 43% of the measurements. The correlation coefficient between heparin dose and HiTT, HR-ACT, and ACT was 0.701, 0.534, and 0.104, respectively. The correlation coefficient between HiTT and the heparin level was 0.560. The average value of the HR-ACT of heparinized blood was significantly lower than that of the ACT (460 ± 115 sec, 531 ± 168 sec; $P < 0.01$). The distribution of ACT values in response to heparin was more scattered than that of HiTT values (Fig).

Figure: Distribution of HiTT vs ACT after heparin administration



Discussion: ACT monitors the functional aspects of heparin anticoagulation rather than the heparin concentration in blood. During CPB, many factors other than heparin concentration affect the ACT, such as hypothermia, hemodilution, or medications like aprotinin or other activators. Our results indicate that HiTT values had less individual variation in response to heparin than did ACT. Also, HiTT had a better correlation with the dose of heparin given than did the ACT or the heparin concentration measured with the Hepcon system.

S342

TITLE: COMPARISON OF POSTOPERATIVE HYPOXEMIA AFTER PROPOFOL VS. HALOTHANE IN CHILDREN

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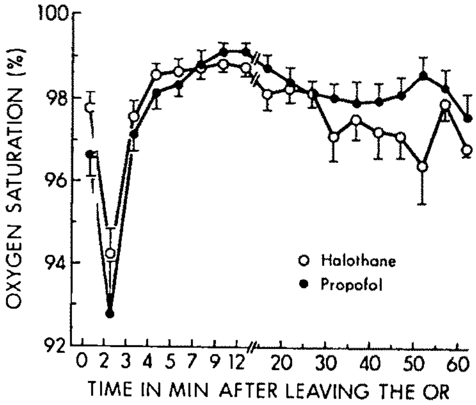
AFFILIATION: Department of Anesthesiology,Washington University School of Medicine,St. Louis, MO 63110

Postoperative hypoxemia has been well documented by pulse oximetry after even minor surgery (1). The duration of hypoxemia is uncertain, but seems to be decreased when the patient is fully awake (2). Awakening is more rapid when propofol vs halothane is used for maintenance of anesthesia (3). This study was designed to test the hypothesis that postoperative hypoxemia is less frequent with propofol than halothane in children.

Methods: We studied 100 children with parental consent and IRB approval. No preanesthetic medications were used. All patients were induced with halothane and nitrous oxide (N_2O) *via* face mask and received morphine 0.1 mg/kg, before tracheal intubation, which was facilitated with atracurium, 0.5 mg/kg. After induction, patients were randomly assigned to receive N_2O, 66% in oxygen (O_2), with either **halothane** 1-3% or **propofol** 50-200 µg/kg/min, adjusted to prevent signs of light anesthesia during the maintenance period. After the surgical procedure was over, neuromuscular blockade was reversed with atropine 10 µg/kg, and edrophonium 1 mg/kg, and the trachea was extubated when patients had recovered airway reflexes and made purposeful movements. All patients breathed 100% O_2 for at least 3 min prior to transport from the OR (time =0). Supplemental O_2 was not given during transport, but administered in the PACU from arrival (time =2) till the patient was awake, or if oxygen saturation values by pulse oximetry (SpO_2) were <90%. The lowest SpO_2 value in each time period is given in fig 1. Chi-square and Student's *t*- tests were used, with a *p* -value of ≤ 0.05 considered statistically significant.

RESULTS: There were no significant differences in age, gender, ASA physical status, type and duration of surgery and anesthesia, or in the mean SpO_2 values (fig 1). While the incidence of hypoxemia (SpO_2 <90%) did not differ between the two groups, significantly more patients in the propofol group were breathing room air 15 min after PACU arrival.



DISCUSSION: Compared to halothane, use of propofol for maintenance of anesthesia, did not decrease the incidence of postoperative hypoxemia in children, but decreased the time supplemental O_2 was required in the PACU.

REFERENCES:(1) Anaesthesia 1965;20:408-420 (2) Anesth Analg 1986;65:267-272 (3) Anesth Analg 1990;71:511-515

S343

TITLE: COMPARISON OF KETOROLAC AND ACETAMINOPHEN IN CHILDREN UNDERGOING BILATERAL MYRINGOTOMIES.

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Bilateral myringotomies with tube placement (BMT) is a very common pediatric surgical procedure.Nitrous oxide (N_2O) and potent inhalational agents are usually used to anesthetize these children, but many appear distressed in the immediate postoperative period, and cannot be readily consoled with rocking, cuddling or feeding. Although pain assessment is difficult in these preverbal children, their behavior after BMT appears to be pain-related and often resolves with rectal acetaminophen (1). In a double - blind, placebo - controlled study, we compared the effects of preoperative oral ketorolac (a nonsteroidal anti - inflammatory drug) and acetaminophen on postoperative pain in children undergoing outpatient BMT procedures.

Methods: The study was performed with IRB approval and written informed parental consent. Thirty minutes prior to induction of anesthesia, 90 children were randomly assigned to one of three oral preanesthetic medication groups: **saline (placebo), acetaminophen** (10-15 mg/kg) or **ketorolac** (1 mg/kg), in a total volume of 5 ml of cherry syrup. No other preanesthetic medications were used. Anesthesia was induced and maintained with halothane and N_20 *via* face mask. In the PACU, a blinded observer assessed the patient's pain using an objective pain scale(OPS) and a 100 mm linear visual analog scale (VAS) at 5 min intervals (2).Patients judged to be in pain received rectal acetaminophen, 10-15 mg/kg.Chi square, Kruskall-Wallis and one-way ANOVA tests were used for statistical analysis, with $p < 0.05$ being considered significant.

Results: There were no significant differences in the three groups with respect to age, gender, weight, ASA physical status, duration of anesthesia and surgery. Times to recovery from end of surgery, median OPS (range) and mean VAS (± SD) pain scores are given in table 1.

Group	Saline	Acetaminophen	Ketorolac
Number (n)	31	29	30
OPS on PACU arrival	1 (0-7)	1 (0-7)	1 (0-7)
5 min	3 (0-8)	1 (0-6)	0 (0-8)*
10 min	3 (0-9)	1 (0-6)	0 (0-9)*
15 min	2 (0-7)	2 (0-7)	0 (0-9)*
VAS on PACU arrival	11 ± 17	8 ± 14	5 ± 11
5 min	22 ± 24	11 ± 15	7 ± 17*
10 min	22 ± 26	16 ± 16	8 ± 14*
15 min	16 ± 17	12 ± 16	9 ± 16*
Analgesic "rescue" Rx	70 %	56 %	38 %*
Postop. emesis (24 h)	11 %	10 %	21 %
SaO_2(%) on arrival	96 ± 2	96 ± 2	97 ± 2
Eye Opening (min)	10 ± 5	12 ± 6	13 ± 6
Discharge (min)	71 ± 28	74 ± 40	69 ± 28

*p <0.05 vs placebo group.

DISCUSSION: Preoperative oral ketorolac, provided better pain relief in the postoperative period than placebo in this population, and did not affect postoperative oxygen saturation, or times to recovery and discharge, or the incidence of postoperative emesis.

REFERENCES: (1) Pain 1987; 31: 147-176 (2) Anesthesiology 1987; 66; 832-835

S344

Title: Ketamine Induced Changes in Cerebral Glucose Utilization in Man as Measured by PET Scan

Authors: P Weir,MD, J Wu,MD, K Tremper,PhD,MD, M Buchsbaum,MD, W Bunney,MD
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Introduction: Ketamine (K) is a phencyclidine (PCP) derivative which produces a dissociative anesthesia. K has also been shown to cause localized changes in cerebral glucose metabolic rate (GMR) in animals[1]. There is little known about K induced changes in regional cerebral GMR in man. K has been shown to bind to a PCP receptor in animals[2] and thus would be expected to show a pattern of changes in cerebral GMR similar to that produced by PCP. We have studied PCP abusing patients with Positive Emission Tomography (PET) and found cerebral GMR to be decreased in the thalamus, limbic system, and basal ganglia and increased in the cerebellum. The purpose of this study was to determine whether K produces changes in regional cerebral GMR similar to those shown to be produced by PCP.

Methods: This study was approved by the institutional review board. Healthy volunteers were used for this study. Each was seated in position for the preformance of the continuous performance test (CPT). A loading dose of 0.12 mg/kg of K was given followed immediately by an infusion of 0.24 mg/kg/hr. 20 min after the initiation of the infusion ^{18}F-2-deoxyglucose (FDG) was given. The K infusion was continued throughout a 30 min period during which the subject was given the CPT. A PET scan was then performed obtaining 9 planes parallel to the canthomeathal line. Scans were transformed to GMR according to the model of Sokoloff. Analysis was caried out on the relative GMR, expressed as the rate of the region of interest divided by the GMR of the whole brain. The data were then compared to data from control subjects using ANOVA. The data presented are the mean ± s.d. of the difference in GMR for each brain region of K and PCP subjects from the control GMR. The zero line is the age and sex matched control value for each region.

Results: Seven male subjects were studied. The results of a three way ANOVA with age and sex matched controls compared with similar data obtained from PCP users is shown in figure 1. As shown K produces a pattern of changes in regional cerebral GMR similar to that produced by PCP.

Conclusion: K, in low dose, produces changes in local cerebral GMR similar to those seen in PCP users, differing only in the white matter and cerebellum. This offers further evidence that ketamine is acting on PCP receptors.

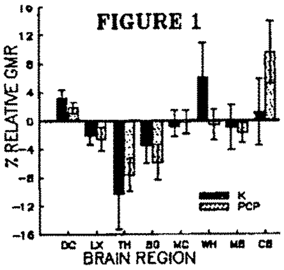
FIGURE 1

DC, dorsal cortex, LX, limbic system, TH, thalamus, BG, basal ganglia, MC, medial cortex, WH, white matter, MB, midbrain, CB, cerebellum.
GMR - glucose metabolic rate

References:
1. J Cereb Blood Flow Metab 7:806-811, 1987
2. Proc Natl Acad Sci USA 76 (10):5371-5376, 1979

S345

TITLE: THE EFFECT OF EXOGENOUS CATECHOLAMINES ON THE MEASUREMENT OF PLASMA CATECHOLAMINE CONCENTRATIONS

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Plasma catecholamine concentrations (PCC) are frequently measured during cardiovascular and metabolic investigations. High performance liquid chromatography (HPLC) has made these measurements easier to perform. To better interpret the results, we examined whether (a) drugs used in clinical practice, specifically synthetic adrenergic agonists and antagonists, interfere with the measurements, (b) there is any difference between mixed venous and arterial PCC.

PCC's were measured using the method of Althaus et al. (1). Catecholamines were extracted from plasma with acid washed alumina elution. This resulted in an 82 ± 5% recovery for the various catecholamines. Separation was with a Bioanalytic Systems Biophase OD2 Column (temp 35°C) using a mobile phase of octyl sulfate, NaEDTA, monochloroacetate and acetonitrile at a flow rate of 1.5 ml/min. A Waters Model 590 pump injector, Wisp 710B, and electrochemical detection at a 0.7 (+) potential and 1.0 nA sensitivity were used. 3,4 Dihydroxybenzylamine was used as the internal standard (IS).

In-Vitro Studies: Pure drug, alone or mixed with plasma and subjected to the extraction procedure, was analyzed. Commonly used adrenergic agonists and antagonists were studied. Acetominophen, which interferes with urinary catecholamine assays (2) was also examined. In-Vivo Studies: Arterial blood samples were obtained from 14 surgical ICU patients not receiving and from 39 receiving adrenergic agents or acetominophen. In an additional 12 patients, mixed venous and arterial blood samples were obtained simultaneously. The mixed venous samples were obtained from the pulmonary artery. This study was approved by the IRB of the Columbia-Presbyterian Medical Center. Informed consent was not required.

Results were expressed as relative retention times (retention times of drug/retention time of IS). In-vitro and in-vivo, the relative retention times (RT) were the same, viz. 0.81 for epinephrine (E), 0.56 for norepinephrine (NE), and 1.56 for dopamine. RT for acetominophen was 1.12 in-vitro and 0.66 in-vivo. Phenylephrine's peak (RT - 0.80) coincided with that of E. Isoproterenol's RT was in excess of 16.00. Dobutamine produced no in-vitro but an in-vivo peak (RT 0.63). Labetalol had no in-vitro but multiple in-vivo peaks (0.77, 0.73, 0.70), likely caused by metabolites (3). Propranolol, ephedrine, and esmolol were not detected. The mixed venous NE & E concentrations (863 ± 327 and 1317 ± 2514 pg/ml), respectively were not significantly different than the arterial ones (837 ± 306 and 1122 ± 2074 pg/ml).

Many of the synthetic drugs appeared on the chromatogram. Their RT's were different in-vitro and in-vivo than those of the endogenous catecholamines. Phenylepinephrine was the only exception, in that it could interfere with the quantitation of E. In very ill patients, there were no significant differences between arterial and mixed venous PCC, which were equally high.

Although this study only examines what occurs with one analytic method, it points out the importance of examining the effects of synthetic adrenergic agents and acetominophen on PCC measurements.

References
1. Anesthesiology 60:440-447, 1984.
2. Annals Clinical Biochemistry 25:538-544, 1980.
3. Clinica Chimica Acta 150:111-117, 1985.

S346

APPLE JUICE 2-3 HOURS PREOPERATIVELY DOES NOT AFFECT PERIOPERATIVE BLOOD GLUCOSE CONCENTRATIONS IN PEDIATRIC PATIENTS

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Introduction: Although all anesthesiologists concur that a preoperative fast is a prerequisite for elective procedures, few agree on the duration of fasting, and whether a glucose containing infusion should be administered intraoperatively to prevent hypoglycemia. The purpose of this study is to (1) compare perioperative blood glucose (BG) concentrations in children who are allowed to drink apple juice 2-3 hrs prior to the induction of anesthesia to those following routine NPO orders, (2) determine the safety of a modified preoperative fasting policy.

Methods: Healthy, unpremedicated children, ages 1-10 years, scheduled for elective outpatient surgery were studied. Informed consent and institutional approval for the study were obtained. All patients had BG determinations preoperatively on admission, during induction of anesthesia, and at conclusion of surgery using Glucometer II. Patients were randomly assigned to one of two groups. All patients did not ingest solids after midnight. Children in Group A were encouraged to drink clear liquids up to 6 h prior to surgery. Group B patients ingested up to 10 cc/kg of apple juice 2-3 hours prior to the induction of anesthesia. Following induction of anesthesia, gastric contents were aspirated and volume and pH were recorded. All patients received Lactated Ringer's solution intraoperatively, unless hypoglycemia (BG < 50 mg/dL) was identified, in which case D2.5LR was administered.

Results: See Tables 1 and 2

Table 1: Age distribution, duration of fasting, BG concentrations, and gastric fluid volume and pH in Groups A and B

	Age (m)	NPO duration (h)	Preop.BG (mg/dL)	Ind.BG (mg/dL)	Postop.BG (mg/dL)	Gastric fluid Vol(ml)	Gastric fluid pH
Group A (n=113)							
mean	49.3	13.1	79.7	79.7	110.9	1.43	1.38
± SD	28.4	3.0	14.0	16.8	30.5	2.87	0.2
Group B (n=71)							
mean	42.1	2.87	78.6	81.8	114.0	1.90	1.46
± SD	20.6	0.71	15.7	18.4	25.6	3.35	0.09

Table 2: Incidence of perioperative decrease or no change in Blood Glucose concentration in Groups A and B

	Age (m)	NPO duration (h)	Preop BG (mg/dL)	Ind BG (mg/dL)	Postop BG (mg/dL)
Group A (n=59)					
mean	45.9	13.2	83.5	73.1	105.7
range	15–127	4.3-18.3	58-113	41-101	59-181
Group B (n=37)					
mean	42.1	2.82	82.5	77.1	114.3
range	13-88	1.58-4.17	53-126	54-134	67-183

Discussion: This study confirms that gastric fluid pH and volume are independent of the duration of the clear liquid fast beyond two hours. Although clear liquids ingested 2-3 hours prior to induction of anesthesia provided a decrease in irritability of children and improved hydration, both groups of patients showed a similar pattern of BG changes perioperatively. It is concluded that a drink of apple juice 2-3 hours prior to surgery does not significantly affect perioperative glucose homeostasis in pediatric patients.

S347

Title: TRANSCRANIAL DOPPLER SONOGRAPHY INDICATES CRITICAL BRAIN PERFUSION DURING HEMORRHAGIC HYPOTENSION IN DOGS

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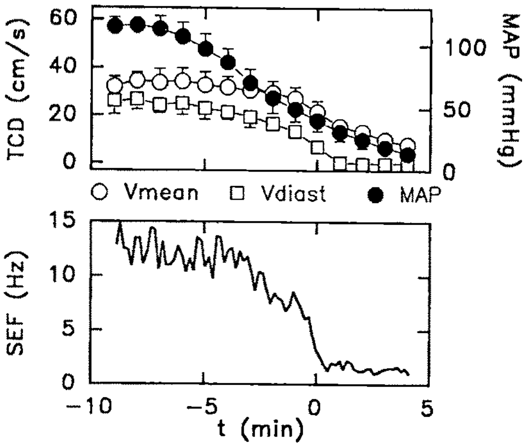
This study investigates the effects of hemorrhagic hypotension on cerebral blood flow velocity using transcranial Doppler sonography (TCD) in correlation to brain electrical activity (EEG).

Methods: Following Institutional Animal Care Committee approval, 8 mongrel dogs were anesthetized with isoflurane and catheters were placed into both femoral arteries and veins for mean arterial blood pressure (MAP, mmHg) measurement, blood withdrawal and drug administration. Brain temperature, arterial blood gases and pH were maintained constant. A pulsed TCD-probe (2 MHz, Transpect ™, Medasonics) was placed on the dura via a temporal bone window to measure mean (Vmean, cm/s) and diastolic blood flow velocity (Vdiast, cm/s) in the middle cerebral artery. EEG was recorded from temporo-parietal recording sites vs. a frontal reference. Isoflurane was then discontinued and all animals received fentanyl (bolus:25µg/kg iv;infusion:50 µg/kg/h iv) plus 50% N_2O/O_2 during 30 min of equilibration. Following recording of baseline data, the stopcock of one femoral artery was opened and the dogs hemorrhaged. Zero time was determined for each dog when diastolic flow velocity decreased 50 %.

Results: Changes in blood flow velocity and EEG spectral edge frequency (SEF) with decreasing MAP are shown in figures 1 and 2. Vmean did not change within the MAP range of 115±7 to 49±9 mmHg. Below 49±9 mmHg, decreases in Vmean and Vdiast were associated with a shift of the EEG to lower frequencies. Brain electrical silence occured at a MAP of 31±7 mmHg, paralleled by a loss of the diastolic flow velocity pattern.

Discussion: Vmean was constant during the decline of MAP to a level of 49±9 mmHg. This suggests autoregulation of cerebral blood flow. Brain electrical silence occured at the same time as the loss of diastolic flow. This indicates that flow velocity patterns and neuronal viability are closely associated.



S348

TITLE: AUTOLOGOUS BLOOD AFTER CARDIOPULMONARY BYPASS ALTERS HEMOSTATIC AND THROMBELASTOGRAPHIC PARAMETERS

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INTRODUCTION: Heparinized autologous blood reinfusion (HABR) after cardiopulmonary bypass (CPB) decreases prolonged partial thromboplastin times (aPTT) and increases platelet counts (PC).[1] This study examined the influence of HABR on coagulation, fibrinolytic and thrombelastographic (TEG) variables after CPB.

METHODS: Following institutional approval and informed consent, 20 adult patients undergoing primary coronary revascularization were studied. After heparinization, and prior to CPB, blood was removed (4.9 cc/kg mean) via an indwelling central line into a non-CPDA plastic transfer pack unit (Fenwal #4R2024) and kept at room temperature. HABR was carried out after protamine infusion. The following assays were performed before and 10 minutes after HABR: hemoglobin (HB), prothrombin time (PT), aPTT, PC, thrombin time (TT), 1:1 TT, fibrinogen (FIB), plasminogen (PLG), D-dimers (DD), and activated clotting time (ACT). TEG (Haemoscope Corp., Morton Grove, IL) parameters, defined previously[2], were obtained via a computer analysis/acquisition system developed in this laboratory.

RESULTS: A statistically significant difference, utilizing the Wilcoxon signed ranks test ($p < 0.05$), was noted in HB, PC, PT, aPTT, FIB, PLG, and the following TEG parameters: MA, A60, and A60/MA. No significant differences were noted in TT, 1:1 TT, ACT, DD, or other TEG parameters (R time, RK time, and angle).

DISCUSSION: Our data supports previous work that HABR post-CPB increases the PC and decreases aPTT. A new finding is that clot strength as assessed by TEG was significantly increased with HABR, as indicated by increases in MA, A60 and A60/MA. This improved clot strength is most likely due to PC increases observed after HABR. Another new finding is the increase in PLG. This PLG increase observed with HABR may partially correct PLG decreases known to occur during CPB.[3] Although increased PLG could theoretically enhance fibrinolytic activity this was not detected by TEG fibrinolytic parameters or changes in a plasma marker of fibrinolysis (DD). The influence of this increase in PLG on the balance between clot formation and clot lysis in the post-CPB period requires further study.

REFERENCES:
1) J Thorac Cardiovasc Surg 74:4-10, 1977
2) Anesth Analg 64:888-896, 1985
3) Semin Thromb Hemost 11:281-292, 1985

S349

TITLE: Less Anesthetic is Required to Tolerate a Laryngeal Mask Airway Than an Endotracheal Tube
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The laryngeal mask airway (LMA) developed by Brain et al[1] to provide an airway during anesthesia, bypasses potentially obstructing oral and pharyngeal structures but does not enter the larynx or trachea. A putative advantage of the LMA is the lower dose of anesthesia required for tolerance of the LMA compared to an endotracheal tube (ETT). In this study we tested in patients whether lower alveolar isoflurane is required to prevent reaction to the LMA than to an ETT.

METHODS: The study was approved by our institutional Human Research Committee. We studied 20 (11 male), unpremedicated, nonsmoker ASA I or II patients aged 18-40 years scheduled for superficial or extremity operations expected to last > 1 hour. They were assigned randomly and equally for airway maintenance with LMA or ETT. LMA patients were anesthetized with a propofol→ insert LMA→N_2O/isoflurane sequence. ETT patients received a propofol→vecuronium (0.015 $mg.kg^{-1}$ IV)→ succinylcholine (1.5 $mg.kg^{-1}$ IV)→insert ETT→N_2O/isoflurane sequence. Once either airway was in place, no additional neuromuscular blocking drugs were given and patients breathed spontaneously throughout anesthesia. At the end of surgery, N_2O was discontinued (end-tidal < 3.0%) and the end-tidal isoflurane (F_E·Iso) was adjusted to 0.8 ± 0.05 vol.%. If no reaction to the appliance was apparent (coughing, gagging, head or purposeful movement) at F_E·Iso 0.8%, we decreased F_E·Iso by 0.1% steps until a reaction occurred, maintaining F_E·Iso constant for at least 5 min. at each level. The F_E·Iso at which a response occurred was interpreted as the airway reaction point for statistical purposes. Gas concentrations were measured with a Raman scatter analyzer.[2] Statistical analysis was by Wilcoxon's rank sum test for anesthetic concentrations, Fisher's Test to examine for sex bias in allocation to LMA or ETT groups, and Student's "t" Test for other data.

RESULTS: Two ETT patients were excluded, one because tonic muscle activity precluded determination of a reaction point and one because of narcotic administration.

The reaction point for LMA was 0.35% F_E·Iso and for ETT it was 0.55% F_E·Iso , significantly different, $p < 0.001$. The groups did not differ for age, sex distribution, propofol dosage, P_E·CO_2, duration of N_2O exposure or time at F_E·Iso before reaction to the LMA or ETT occurred.

DISCUSSION: We substantiated the clinical impression that the LMA is tolerated to lighter levels of anesthesia than an ETT. When either appliance can be used safely for airway maintenance, the LMA may allow lower anesthetic doses to be given throughout surgery. More prompt recovery from anesthesia should be possible.

REFERENCES
1. Br J Anaesth 55:801, 1983. 2. J Clin Monit 2:215, 1986.

	LMA	ETT
Age, years	30.8 ± 9.6	26.1 ± 8.1
Gender Male (n)	7	4
Female (n)	3	4
Propofol - $mg.kg^{-1}$	3.1 ± 1.04	3.5 ± 0.88
F_E·Iso at Reaction Point	0.35 (0.2-0.51)	0.55 (0.4-0.7)

Mean ± SD except F_E·Iso = mean (range); n = Number

S350

Title: **MALIGNANT HYPERTHERMIA INDUCTION IN SUSCEPTIBLE SWINE FOLLOWING EXPOSURE TO ORGANON 9426**
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Introduction: Organon 9426, (1-[(2B,3a,5a,16B,17B)-17(acetyloxy-3-hydroxy-2-(4-morpholinyl)-androstan-16-yl]-1-2(propenyl) pyrrolidinium bromide), [1-5] was studied for physiological effect as a muscle relaxant. These studies were designed to evaluate the dose response of each pig, the continuous infusion dose required to maintain a 90% neuromuscular block and then to evaluate the Malignant Hyperthermia triggering potential of ORG 9426.

Methods: Protocol #88050-8 was approved by the TTUHSC-IACUC. Ten MHS (wt 50.93 Kg) and eight control pigs (wt 53.55 Kg) were used. Thiopental (22mg/Kg) was used for sedation with added increments as needed. The animal was intubated and mechanically ventilated with 33% O_2:67% N_2O. Sterile surgical cutdowns were completed to the external jugular vein and the Opticath Swan-Ganz catheter (7F) was inserted and advanced to the wedge position. The internal carotid artery was exposed and the Millar Mikro-tip catheter Pressure Transducer was inserted and advanced to the apex of the left ventricle. The femoral artery was exposed and a 16G catheter was inserted retrograde 10-12cm. A Grass FT10 transducer, HSE neuromuscular monitor and HSE neurostimulator set at supramaximal (TO4)(0.2ms,2Hz,15sec) was used to stimulate the left peroneal nerve and record twitch response.

Results: ORG 9426 had an onset time of45.6 sec in control pigs and an onset time of 83.4 sec in MHS pigs. Duration 90 for ORG 9426 was 7.21 min in control pigs and 12.0 min in MHS pigs. The duration 90 of ORG 9426 appears to be shorter in pigs than in humans. 25 to 75% recovery rate was 2.84 min in control pigs and 4.59 min in MHS pigs. Control pigs required 109.9 ug/kg/min and MHS pigs required 72.4 ug/kg/min infusion of ORG 9426 to maintain a 90% block. The fact that MHS pigs only required 66% of the infusion dose to maintain a 90% block suggests that there is a marked difference in the neuromuscular effect of ORG 9426 in MHS vs control pigs. Alkalosis gave a slight increase (0.09%) in the ORG 9426 block in control pigs. Acidosis gave a 2.5% increase in the degree of neuromuscular block from ORG 9426. Both alkalosis and acidosis produced a decrease (5.8 and 5.0%) respectively in MHS pigs. From the Core Temperature Data (Organon 9426) it is obvious that the MHS Pigs treated with a 90% blocking dose infusion of Org 9426 exhibited a significantly greater ($P < 0.01$) decrease of core temperature from 37.32°C down to 36.88°C with continued cooling during halothane and succinylcholine to a final core temperature of 36.02°C. Rectal temperature data showed a similar decrease.

Discussion: Organon 9426 does not trigger MH in MH susceptible pigs. Organon 9426 does not have any appreciable side effects that would inhibit its use as a muscle relaxant. There was a significant decrease in arterial and venous *p*H in MHS pigs during the infusion of ORG 9426. The precise reason for the decrease in blood pH was not apparent from this data. Organon 9426 appears to be a prime candidate of a muscle relaxant which will prevent the development of the MH Syndrome.

References: (1) Brit J Physiol (1989) 63(4):400-410. (2)Anesthesiol (1989) 71(3A):A774. (3) Anesthesiol (1989) 71(3A):A773. (4) Anesthesiol (1989) 71(3A):A772. (5) Brit J Anaesth (1989) 62(2):225P-226P.

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S351

TITLE: **ONSET OF ORG 9426: A COMPARISON WITH ATRACURIUM AND VECURONIUM**

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ORG9426 is a steroidal non-depolarizing neuromuscular blocker with an intermediate duration of action. This study was designed to compare this drug in a case control manner with the other two commonly used intermediate acting relaxants, atracurium and vecuronium with regard to onset of effect.

Methods: ASA Class I-II patients undergoing elective surgery who had given informed consent to this IRB approved investigation were studied. Fifteen patients received either atracurium or vecuronium. Acceptable patients achieved 90 ± 8% blockade. Each patient was paired with a patient from a group of 60 who had received ORG9426. Pairing was based on degree of maximum blockade achieved. Where possible, patients were matched for age, sex and weight.

After premedication with diazepam 100-150 mcg/kg p.o., anesthesia was induced with sodium thiopental 4-8mg/kg and fentanyl 4-8mcg/kg. Intubation was accomplished under enflurane 2%ET and N2O/O2 in a 60:40 ratio. No muscle relaxant was given prior to intubation. Enflurane concentration was reduced to 1%ET (Datex-PB) and held stable for 15 minutes. Patients then received vecuronium 0.02mg/kg, atracurium 0.12mg/kg or ORG9426, average dose 0.18mg/kg. Adductor pollicis function was monitored with train of four stimulation of the ulnar nerve at the wrist every 12 seconds. Time to 5%, 50%, 75%, and 90% of maximum block was calculated for each drug. Comparisons between atracurium and its 9426 control group and vecuronium and its 9426 control group were made. Atracurium and vecuronium onset times were also compared. Statistical analysis was by repeated measures ANOVA, P<0.05 was considered significant.

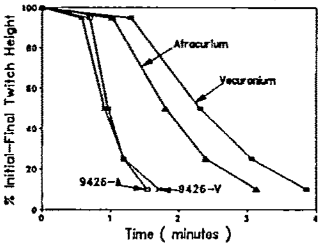
Results: Twenty-four patients were selected. There were six patients in each group. Paired patients had similar age, sex and weight distributions. Maximal first twitch depression was closely correlated between groups (Table 1). Atracurium and its control group averaged 90% block while vecuronium and its control group reached 92% block. Onset of block was significantly faster for ORG9426 than either atracurium or vecuronium. Atracurium's onset was somewhat more rapid than vecuronium (Figure 1).

Discussion: Onset of ORG9426 is approximately twice as fast as the other available intermediate acting blockers. Peak blockade of 90% was achieved within 90-100 seconds. This drug is promising in situations where rapid onset of neuromuscular blockade is required.

Table 1. Dose vs. % Block

Drug	Dose (mg)	% Max Block
Vec.	0.02	91.8(7.8)
9426 V	0.18	91.7(8.5)
9426 A	0.17	89.7(4.8)
Atr.	0.12	90.2(6.5)

Figure 1. Onset of 9426 vs. atracurium and vecuronium.



S352

TITLE: STABILITY OF DATEX NEUROMUSCULAR MONITORING IN ANESTHETIZED INFANTS

AUTHORS: S.K. Woelfel, M.D., B.W. Brandom, M.D., F.X. McGowan, M.D., D.R. Cook, M.D.
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Introduction: The Datex neuromuscular transmission monitor (NMT) integrates the evoked electromyogram (EEMG) from train-of-four (TOF) stimulation. Evoked responses are referenced to the initial response (T1) and TOF are calculated. Frequently, the EEMG T1 at the end of an anesthetic does not return to its initial value, although TOF equals 100%. The goal of this study was to define factors that might contribute to this shift in baseline.

Methods: Following institutional approval and parental consent, 24 infants (ASA 1 or 2) aged 3-6 mo were studied. Anesthesia was induced with N20, 02, halothane (0-3%). Halothane (ET 1.0%) was maintained after an IV catheter was placed, 10 µg/kg of atropine and 1 µg/kg of fentanyl were administered. Palmar temperature was recorded at the beginning and end of the monitoring period. Initial calibration of the NMT documented supramaximal stimulus (mA), peak amplitude (mV), and duration of positive EEMG deflection (ms). After bolus and titrated infusion of a nondepolarizing neuromuscular blocker produced 95 ± 4% neuromuscular block, spontaneous or pharmacologically induced recovery produced constant T1 with TOF of 100%. Final T1 height was recorded at that time. The EEMG was then recalibrated; supramaximal stimulus, amplitude and duration of positive EEMG deflection were recorded. The amount of time halothane was administered prior to initial and final calibrations was noted. Paired-sample *t* tests were used to determine the differences between initial and final values of the above parameters. Correlation analysis was used where appropriate. Results were presented as mean ± SD (range).

Results: In these 24 patients (4.7 ± 1.3 mo; 62.6 ± 3.8 cm; 6.9 ± 1.1 kg; 0.36 ± 0.04 m^2) T1 returned to at least 90% of the initial value in 10, and to 95% in only 6. Final T1 averaged less than initial T1 by 17 ± 12% ($p<0.01$). Peak amplitude of EEMG decreased by 0.6 ± 0.4 mV ($p<0.01$). There was a significant correlation, R=0.63, between the changes in T1 and amplitude ($p<0.01$). Duration of exposure to halothane prior to initial calibration averaged 10.3 ± 3.4 (5-15.5) min. Duration of halothane exposure between calibrations averaged 112 ± 69 (43-311) min. There was no significant correlation between either of these times and the change in T1 or amplitude. Palmar temperature increased 0.8 ± 1.4°C ($p<0.02$). There were no significant changes in supramaximal stimulus or duration of positive EEMG deflection.

Discussion: Change in supramaximal stimulus and duration of the positive deflection do not appear to be significant factors contributing to the change in T1 with time during anesthesia. Similarly there was no decrease in temperature of the hand, which could have produced a decrease in neuromuscular function (1). Because the T1 value produced by the Datex monitor is the rectified integration of the EEMG, it is to be expected that the change in T1 correlates with the change in amplitude of the EEMG. Decreased amplitude could be related to decreased release of acetylcholine (2), increased skin impedance or decreased depolarization of the muscle membrane. That neither the decrease in T1 nor in amplitude correlated with the duration of nerve stimulation, suggests fatigue was not a factor in this study. It is expected that exposure to anesthetic could decrease EEMG (3), but the time course of this effect was not demonstrated in this study.

References:

1. Anesthesiology 71:381-384,1989
2. Anesthesiology 73:A872,1990
3. Computerized EMG Monitoring. Malherbe Pub Group,1988

S353

Title: DO THE RESIDENT APPLICANTS WANTED MOST BECOME THE BETTER RESIDENTS?

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Introduction: Considerable effort is spent selecting prospective anesthesia residents. Resident applicants are screened, interviewed, and then ranked on a list submitted to the anesthesia resident match. Presumably anesthesia residency programs base their rankings on their estimate of any given applicant's potential to become a "good" anesthesiologist. If resident selection non-random, then there should be a relationship between the resident rankings before residency and clinical performance during residency. The purpose of this study was to determine if there was any correlation between match list rankings, NBME scores, or interview scores and resident clinical evaluations.

Methods: Our anesthesia resident 'selection process is based upon a scoring system comprised of 4 interview scores and the NBME part 1 score. The interview scores are further normalized to each individual faculty member's average interview score.

Each quarter all residents are evaluated and scored by the faculty according to published ABA resident evaluation criteria.

The current PGY4 residents (selected in the 1987 resident match), PGY3 residents (selected in the 1988 resident match), and PGY2 residents (selected in the 1989 resident match) were all ranked according to their match list position, part 1 NBME score, average interview score, and their mean clinical evaluation score. The PGY2 clinical evaluation score was based on 2 evaluations, the PGY3 score on 6 evaluations, and the PGY4 score on 10 evaluations. The correlation of match list position, NMBE score, or interview score with clinical evaluation was evaluated by Spearman rank correlation coefficient. A probability value <0.05 was considered significant.

Results: For the PGY2 resident class, no parameter correlated with clinical performance. For the PGY3 resident class, only interview score correlated with clinical performance ($P<0.02$). For the PGY4 resident class, only match list rank correlated with clinical performance ($P<0.05$). The rankings for the PGY3 residents are listed in Table 1.

Discussion: It is reassuring that the resident and selection process is non-random. The failure of any parameter to be associated with PGY2 performance may be due to only 2 evaluations or the fact that PGY2 residents are still on a steep portion of their learning curve.

TABLE 1

PGY 3 RES.	CLIN EVAL RANK	MATCH LIST RANK	INTER-VIEW RANK	BOARD SCORE RANK
A	1	2	1.5	6.5
B	2	1	1.5	1
C	3	6	4	8
D	4	11	8.5	4.5
E	5	4	6.5	10
F	6	5	5	2
G	7	3	3	9
H	8	9	11	3
I	9	8	6.5	6.5
J	10	7	10	4.5
K	11	10	8.5	11

1 = best; 11 = worst

S354

Title: CHANGES IN $S\bar{v}O_2$ DO NOT PREDICT CHANGES IN THERMODILUTION CARDIAC OUTPUT

Authors: DH Wong, PharmD., M.D., P. Weir, M.D.,
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INTRODUCTION

Mixed venous oximetery ($S\bar{v}O_2$) is often used to monitor changes in cardiac output (CO). This assumes that patients SaO_2, Hb or O_2 consumption is stable; then changes in $S\bar{v}O_2$ ($\Delta S\bar{v}O_2$) should reflect changes in CO (Δ CO)(1).

Using a change in one physiologic parameter to predict a change in another, means that the first parameter is being used as a diagnostic test for the second. Therefore, the accuracy of $\Delta S\bar{v}O_2$ to predict Δ CO should be quantifiable in terms of sensitivity and specificity. Other authors have anecdotally reported that 10% $\Delta S\bar{v}O_2$ are related to Δ CO but actual sensitivities and specificities have not been reported (2).

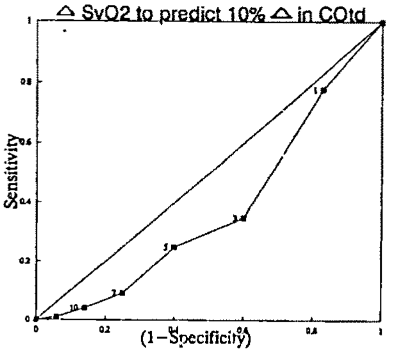
The purpose of this study was to determine the specificity and sensitivity of $\Delta S\bar{v}O_2$ to predict Δ CO.

METHODS

$S\bar{v}O_2$ was measured with either Abbott Oximetrix® or Edwards Sat-2® $S\bar{v}O_2$ catheters in ICU patients. CO was measured by thermodilution with 10cc of room temperature injectate in triplicate. Each pair of CO_{TD} and $S\bar{v}O_2$ measurements was compared with the preceding measurements. The change in $S\bar{v}O_2$ needed to predict a $\geq$ 10% Δ CO was tested at cutoff values of 1,3,5,10, and 15% Sat differences in $S\bar{v}O_2$. The sensitivity and specificity at each cutoff was used to create a receiver operator characteristic (ROC) curve.

RESULTS

148 measurement sets were made in 22 patients. CO changed $\geq$ 10% 74 times; CO increased 37 times and CO decreased 37 times. The ROC for different $S\bar{v}O_2$ thresholds to predict ΔCO_{TD} is shown in figure 1.



DISCUSSION

Our ROC curve shows that $\Delta S\bar{v}O_2$ did not predict Δ CO well. The most likely reason for this is that the assumptions that SaO_2, Hb, and O_2 consumption are constant between consecutive CO determinations may be invalid.

REFERENCES

1. Int Anes Clinic 1987; 25(3):113-136.
2. Critical Care Medicine 1988; 16(5):495-498

S355

Title: USE OF PLACEBO PCA BY PATIENTS RECEIVING EPIDURAL FENTANYL ANALGESIA

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Introduction We conducted a randomized, double-blind, placebo-controlled comparison of epidural fentanyl and iv morphine by patient-controlled analgesia(PCA) in post-thoracotomy patients. This afforded a unique opportunity to observe the patient's use of the PCA device independent of pharmacological influences.

Methods After institutional approval and written informed consent, a thoracic epidural infusion starting at 5 cc/hr and an iv PCA device delivering 1 ml/demand were established for 36 post-thoracotomy patients, who were assigned by random number to either Group I--50 ug/cc fentanyl in epidural, saline in PCA, or Group II--saline in epidural, morphine 1 mg/cc in PCA. Group assignment was unknown to the patients, nurses and a physician evaluator. For 3 days after surgery, during the hours of 0700 and 1900, analgesia was evaluated 2 hourly by Visual Analog Scale(VAS) at rest and during coughing, and Verbal Rating Scale(VRS) of pain relief. Total Pain Relief(TOTPAR) was derived. Correlation between TOTPAR and volume of PCA used was evaluated by Kendall's tau--a rank-based correlation factor, with statistical significance at $p< 0.05$.

Result The mean(±s.d.) volume of PCA saline used by Group I patients (receiving epidural fentanyl) was 39.8±35.1, 34.1±29.8, 31.0±33.7 ml during the 3 days. The volume of saline was not correlated with patients' expressed pain relief(TOTPAR) (Table 1).

Discussion Since the PCA device delivered only placebo in group I, the extent of use was governed by psychological forces. The lack of correlation with expressed pain relief (TOTPAR) suggests that patients did not seek to achieve complete analgesia, but used PCA to reach an individually determined level of expected comfort. Further study on the psychological aspect of using PCA is warranted.

Table 1. Correlation between TOTPAR and volume of saline used via PCA

	Kendall's *tau*	*p*=
Day 1	-0.015	.468
Day 2	-0.170	.175
Day 3	0.270	.060

S356

TITLE: HEMODYNAMIC EFFECTS OF URAPIDIL IN CHRONICALLY INSTRUMENTED DOGS WITH CORONARY ARTERY OCCLUSION

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Urapidil is used intra- and postoperatively for the treatment of acute hypertension in patients undergoing coronary bypass surgery.(1) It has been demonstrated previously in acutely instrumented dogs that urapidil improves the systolic function of ischemic myocardium.(2) Whether this beneficial effect is due to a reduction in myocardial oxygen demand or an increase in myocardial oxygen supply is not clear. We examined the hemodynamic effects of urapidil in chronically instrumented dogs with single vessel coronary occlusion.

Five dogs were chronically instrumented to obtain measurements of left atrial (LAP), left ventricular and aortic blood pressures, cardiac output (CO), heart rate (HR), blood velocity in the left anterior descending (LAD) and circumflex (CX) coronary arteries and regional wall thickening fraction (WT) in both perfusion areas. An Ameroid constrictor was placed around the CX to induce complete vessel occlusion within three weeks. Experiments were started two weeks later. After baseline hemodynamic measurements, urapidil was infused in two increasing doses (0,1 mg/kg bolus + 0,3 mg/kg/min and 0,5 mg/kg bolus + 1,5 mg/kg/min) while the animals were resting on their right side. In one dog, tracer microspheres were used to measure regional blood flow distribution during control and following the high dose of urapidil.

Table 1 shows that rapidil caused a dose dependent decrease in mean arterial blood pressure (MAP) and systemic vascular resistance (SVR). CO, LAP, left ventricular rate of pressure rise (dP/dt max), and WT in both the LAD and CX area remained unchanged. Table 2 shows a slight increase in blood flow to the normally perfused as well as to the collateral dependent myocardium. The endo-to-epicardial flow ratio remains preserved in both perfusion areas.

We conclude that urapidil preserves global and regional myocardial function in dogs. In addition, our preliminary results indicate that perfusion to normally and collateral dependent myocardium is slightly improved.

Table 1: Global and regional hemodynamics

	Control	Urapidil 1	Urapidil 2
HR (bpm)	93 ± 11	99 ± 11	106 ± 8
MAP (mmHg)	89 ± 5	83 ± 5 *	73 ± 2 *
dP/dt max (mmHg/sec)	2188 ± 219	2188 ± 234	2063 ± 193
LAP(mmHg)	4 ± 2	3 ±1	2 ±1
CO (L/min)	1.9 ± 0.4	1.9 ± 0.4	1.9 ± 0.4
SVR (mmHg/L/min)	55 ± 9	51 ± 9 *	45 ± 9 *
LAD velocity (KHz)	8 ± 2	9 ± 2	9 ± 2
WT lad (%)	20 ± 2	20 ± 2	19 ± 2
WT cx (%)	29 ± 4	31 ± 5	28 ± 4

Mean ± SEM ; * = $p < 0.05$ vs control

Table 2 : Myocardial perfusion

	Normal (LAD)		Collateral (Cx)	
	Control	Urapidil	Control	Urapidil
Total Blood Flow (ml/100 g /min)	56	81	57	97
Endo- to epicardial	1.5	1.6	2.0	1.8

References
1. Europ J Anesth 2 : 21-27, 1985
2. Basic Res Cardiol 85 : 270 - 278 , 1990

S357

TITLE: CARDIOVASCULAR SUPPORT DURING EPIDURAL AND GENERAL ANESTHESIA: IV PRELOADING OR VASOCONSTRICTORS?

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Introduction: Epidural anesthesia during and after knee replacement reduces the incidence of post-operative thromboembolism.[1] However this operation is carried out in an ageing population in whom CVS stability is desirable. Combined lumbar epidural (LEA) and general anesthesia (GA) has been observed to cause more severe CVS depression than either single technique[2] and the purpose of the present study was to find the most appropriate method of CVS support in such a population.

Methods: With local ethical committee approval and informed patient consent forty five ASA 1 or 2 patients due to undergo major intra-articular knee surgery were studied. Patients with dysrhythmias or on cardioactive drugs were excluded. LEA was induced using 20 ml of lidocaine 2%. After 20 min GA was induced using thiopentone and maintained with O_2 33% in N_2O and isoflurane at an end tidal concentration of 0.5%. The patients were randomly allocated to receive - during the induction of epidural anesthesia - either: An IV preload (500ml Dextran 70 before and 500ml Hartmann's solution during the first 20 min of the block) (group P); or ephedrine 24 mg (group E); or methoxamine 4 mg (group M). All patients received 500 ml of Hartmann's solution during the first 40 min of general anesthesia. HR, ABP, and CO were monitored and recorded every 2 min using the Datascope Accutorr and Accucom respectively and the values between 12 and 20 min were meaned to provide a steady state value during LEA. Values between 10 and 25 min after the induction of GA were meaned to give a value for LEA+GA. Results were analyzed using oneway analysis of variance with Newman-Keuls test, and are reported as mean (SD).

Results: There were fifteen patients in each group and the groups were comparable in age, weight, height and M:F ratio. The results are in the table.

	SAP(mmHg)			CI(L min^{-1} m^{-2})		
	Control	LEA	L+GA	Control	LEA	L+GA
P	137(22)	120(22)	98(17)*	3.0(0.7)	4.3(1.1)	3.4(1.1)¶
E	136(20)	130(24)	114(20)	2.8(0.8)	3.1(0.9)†	2.9(1.0)¶
M	137(28)	135(29)	97(14)*	2.7(0.9)	2.6(1.1)†	2.2(0.7)

	SVRI (DS cm^{-5} m^{2})			LVWI(Kg m m^{-2})		
	Control	LEA	L+GA	Control	LEA	L+GA
P	2949(908)	1777(511)*¶	1944(615)¶	4.5(1.3)	5.8(2.0)¶*	3.8(1.5)
E	3280(791)	2739(765)¶†	2593(1005)	4.3(1.6)	4.4(1.7)	3.6(1.5)
M	3487(1477)	3511(1268)*†	2854(1032)	3.9(1.2)	3.7(1.2)	2.2(0.6)†*

$P<0.05$ * compared to E, † compared to P, ¶ compared to M

Discussion: These results suggest that the three regimens under consideration were equally effective in maintaining blood pressure during LEA, but that this was a result of increased CI in group P and an unchanged SVR in M, E being midway between. When GA was induced CI decreased in P, whereas in M SVRI decreased; in both this produced large significant reductions in ABP. In contrast in group E the induction of GA did not result in much change in either ABP, CO or SVR. LVWI was increased in P during LEA and decreased in M during LEA+GA. Ephedrine appears to offer advantages over preloading or methoxamine in this population.

Reference:

1. British Journal of Anaesthesia 66, 8 (1991)
2. Anaesthesia and Intensive Care 7, 229. (1979)

S358

TITLE: **THIOPENTAL DOES NOT PROTECT AGAINST HEMODYNAMIC RESPONSES TO INTUBATION, EVEN IN LARGE DOSES**

AUTHS: **M. WRONSKI M.D., R. VESELIS M.D., R. REINSEL Ph.D.**

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Burst suppression in the EEG is considered to represent a deep level of CNS depression. At this degree of CNS depression hemodynamic responses to noxious stimuli would not be expected. We investigated whether hemodynamic changes occurred in patients during intubation following the occurrence of burst suppression in the EEG induced by thiopental.

METHODS: With IRB approval, 6 patients (mean age 55) scheduled for craniotomy (n=5) or thoracotomy (n=1) received thiopental infusion at 50-75 mg/min until after intubation was complete. Intubation was performed after burst suppression was seen on the analog EEG signal from frontal and parietal leads at least 50% of the time (mean dose of thiopental at intubation 10.5 ± 2.1 mg/kg, dose to burst suppression: 672 ± 160 mg). Muscle paralysis was induced with vecuronium 0.1 mg/kg. Blood pressure was monitored continuously with an arterial catheter. Statistical analysis was performed using repeated measures ANOVA with orthogonal contrasts.

RESULTS: In all cases mean arterial pressure (MAP) and heart rate (HR) increased significantly during intubation (MAP: $P<0.008$, HR: $P<0.0005$). The mean percent change in MAP after intubation was 143%, while HR increased 124%.

	BASELINE	**PRE-LARYNGOSCOPY**	**POST-INTUBATION**
MAP (SD)	98 (10)	93 (12)	129 (13)
HR (SD)	81 (19)	87 (20)	108 (23)

CONCLUSIONS: Thiopental is commonly the only anesthetic agent used before intubation is performed. Even when enough thiopental is given to produce burst suppression on the EEG, significant increases in MAP and HR occur in response to intubation. Other agents need to be used with thiopental to avoid the hemodynamic changes associated with intubation. Burst suppression in the EEG does not indicate a deep enough level of anesthesia to avoid the hemodynamic changes seen with intubation when thiopental is used.

S359

Title: COMPUTER-ASSISTED VALIDATION OF OBSERVER-RECORDED DATA IN PATIENTS RECEIVING INTRAVENOUS SEDATION

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Introduction: Previous investigations have shown that systematic errors can occur with hand recording of physiologic data during clinical anesthesia.[1-2] The purpose of this project was to evaluate the accuracy of such recordings by a nurse-observer as part of a multicenter study of patients receiving intravenous sedation for the surgical removal of third molars.

Methods: We compared observer- and digitally recorded physiologic data from 100 patients, each subject receiving (double-blind) one of the following IV drug regimens: placebo; midazolam to a clinical endpoint of sedation (M); M + midazolam increments as needed; 1.4 µg/kg fentanyl (F) + M; and F + M + methohexital increments as needed. With the exception of the ECG, which was recorded with a Holter monitor, physiologic measurements (HR, RR, SaO_2, $EtCO_2$) obtained from Ohmeda Biox 3700 and 5200 monitors were digitized at 4 Hz (MacADIOS II, GW Instruments) and recorded by computer (Macintosh II, Apple Computer). Observer recordings were made preoperatively, during sedative drug administration, and every 5 min intraoperatively. Observer- and computer-recorded values were then matched and evaluated for discrepancies. Analysis of variance and chi-square analysis were used for statistical evaluation of physiologic data and error rates by group.

Results: Discrepancies were noted in 1086 of the 6564 data pairs. The vast majority of these variances were inconsequential and caused by small differences in the time of recording and in the averaging algorithms used for visual display and digital data reduction. However, 51 deviations were attributed to hand-recorded errors, and 67 involved digitally recorded artifacts. Error rates were evenly distributed by treatment group except for a tendency toward fewer RR discrepancies in subjects receiving F. Both recording methods yielded identical results with respect to drug-induced changes in cardiopulmonary status.

Discussion: These findings suggest that hand recording of physiologic data can be highly accurate when the observer is not responsible for patient care. Computer-assisted recording of physiologic data is equally satisfactory; however, because the two methods differ in the types of errors to which they are most susceptible, accuracy of data gathering is optimal when both are used concurrently.

References: 1. Anesthesiology 71:385-390, 1989.
2. Anesth Analg 72:S296, 1991.

This study was supported by NIH Contract DE 72568.

S360

Title: EFFECTS OF VOLATILE ANESTHETICS ON DIASTOLIC FUNCTION IN DOG -AN ECHOCARDIOGRAPHIC STUDY

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INTRODUCTION: The effects of volatile anesthetics on systolic ventricular function have been extensively studied, but recently attention was focused on diastolic function. We evaluated the effects of halothane (H), enflurane (E) and isoflurane (I) on diastolic function in dog by using echocardiograph under different concentrations of anesthetics.

METHODS: Twenty-four mongrel dogs weighing 9.8-13.6kg were anesthetized with pentobarbital, intubated and mechanically ventilated with volatile anesthetics and oxygen. Dogs were randomly divided into three groups by inhalational anesthetics; H group (n=8), E group (n=8) and E group (n=8). ECG, left ventricular pressure, pulmonary capillary wedge pressure, phonocardiograph and M-mode echocardiograph were recorded at 0%(control), 1%, 2%, and 3% concentration of each anesthetic. Diastolic function was evaluated by the diastolic time interval (DTI), relaxation function (time constant for isovolumic left ventricular pressure decline (T)) and ventricular filling function (coefficient of stiffness (S) and filling rate at each DTI).

RESULTS: T and S increased significantly with 2% and 3% H and 3% E compared to control. I, however, did not significantly increase T and S. Filling rate decreased significantly at rapid filling time (1%, 2% and 3% H, 2% and 3% E, 3% I) and at atrial contraction time (2% and 3% H, 3% E, 3% I) but no significant change was observed at slow filling time. DTI's did not change significantly with each concentration of anesthetic.

DISCUSSION: H and E depressed ventricular diastolic function with dependent on its concentration, but I depressed least on both relaxation and ventricular filling functions. Compensation for decrease of the early filling with filling at the atrial contraction was not observed during administration of inhalational anesthetics. From this data we suggested that isoflurane is one of choice of anesthetic agent for cardiac patient such as ventricular hypertrophy and heart failure with prolonged relaxation.

REFERENCES: Anesthesiology 73:731-738,1990, Anesthesiology 69:464-471,1990, JACC 9:1189-1193,1987

Time Const(msec)	0%	1%	2%	3%
Halothane	31±6	35±6	40±6*	54±12*
Enflurane	31±5	32±6	36±9	40±6*
Isoflurane	32±9	32±9	33±8	35±7

Stiffness(×100)	0%	1%	2%	3%
Halothane	14±4	15±4	17±4*	18±5*
Enflurane	14±1	14±2	15±2	16±3*
Isoflurane	14±2	14±2	15±2	16±3

mean±SD *p<0.05

S361

Title: EFFECT OF LUMBAR EPIDURAL ANESTHESIA ON PROSTAGLANDIN E_1-INDUCED DIURESIS IN DOGS

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INTRODUCTION: We recently observed that prostaglandin E_1(PGE_1)-induced diuretic effect was abolished in patients under general anesthesia combined with lumbar epidural anesthesia compared with that under general anesthesia alone(1). But the mechanism has not clearly understood. In this study we investigated the mechanism of the decreased PGE_1-induced diuretic effect in dogs under general anesthesia combined with lumbar epidural anesthesia.

METHODS: After the institutional approval of the research protocol, 16 mongrel dogs, weighing 8.0 to 15.0kg, were included in this study, and were divided into 2 groups (A and B, n=8 each). For all dogs, anesthesia was maintained with 1% halothane anesthesia under controlled ventilation. Arterial and pulmonary arterial line was placed. After laparotomy a probe for electromagnetic flowmetry was placed to left renal artery, and bilateral ureters were cannulated and connected to the urine container. In group B, epidural catheter was placed through $L_{1/2}$ space, and epidural anesthesia was performed by using 2% lidocaine without epinephrine, 6ml/hr. During the study, arterial, pulmonary, and central venous pressures and renal blood flow (RBF) were continuously recorded. The first (Before) 1-hour urine was collected after vital signs and urine flow got steady. Then PGE_1 was infused at the rate of 0.5mcg/kg/min and the second (During) 1-hour urine was collected. Mixed venous blood was withdrawn to determine plasma antidiuretic hormone (ADH), creatinine, and sodium levels. Hemodynamic data, urine volume (UV), creatinine clearance (Ccr), fractional excretion of sodium (FE_{Na}), and plasma ADH level were compared between before and during PGE_1 infusion, and between groups A and B. Student's t-test and paired t-test were used for statistical analysis. P<0.05 was considered significant.

RESULTS: The results appear in Table below.

Table. Main results of the study.

	Group A		Group B	
	Before	During	Before	During
MAP (mmHg)	142±21	115±14**	86±23^{++}	63±15**
HR (bpm)	160±21	169±27	94±13^{++}	96±22
SVR$^{\$}$	387±114	273±77**	333±96	244±82**
CO (L/min)	3.0±1.0	3.4±1.1	2.0±0.5^{+}	2.1±0.8
RBF (ml/min)	139±54	170±70**	147±45	128±47*
UV (ml/hr)	225±169	344±139*	141±77	125±136**
Ccr (ml/min)	41±8	45±10	20±4^{++}	11±3*
FE_{Na} (%)	1.4±0.7	3.9±1.6**	3.1±0.9	1.3±0.4**
ADH (pg/ml)	42±28	23±16*	48±30	33±13

(MEAN±SD) *:p<0.05, **:p<0.01 vs Before
+:p<0.05, ++:p<0.01 vs group A.
MAP:mean arterial pressure, HR:heart rate,
SVR:systemic vascular resistance
\$:(*10 dynes*sec/cm^5), CO: cardiac output.

DISCUSSIONS: In dogs under general anesthesa combined with epidural anesthesia did not showed PGE_1-induced diuretic effect, which mechanism is due to decreased Ccr, secondary to decreased perfusion pressure and CO, and decreased FE_{Na}.

REFERENCE: 1.Can J Anaesth 1991;38(suppl):A7

S362

Title: DOSE-RESPONSE RELATIONS OF INTRATHECALLY ADMINISTERED MORPHINE IN RATS

Authors: H.Yamaguchi, MD; S.Incmata, MD; S.Watanabe, MD.

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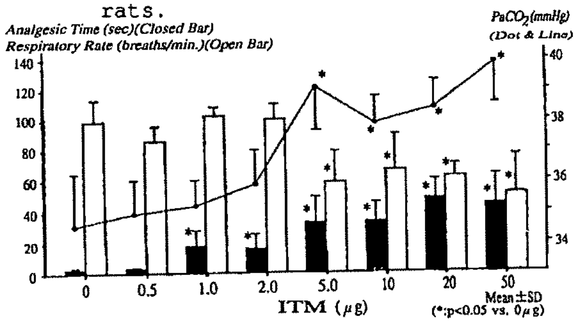
INTRODUCTION: The practice of intrathecal morphine (ITM) is clinically used mainly for relief of postoperative pain, but which often accompanies with respiratory depression. Recently we reported the minimal effective ITM doses for pain relief after hysterectomy(1) and cholecystectomy(2). In this study we investigated the dose-response relations of ITM in rats to find a dose range of ITM with effective analgesia and without respiratory depression.

METHODS: After institutional approval of the study protocol, 18 adult male Wistar rats, weighing 325-385g, were divided into group A and B (n=9 each). All rats had chronic intrathecalcatheters, polyethylene tube, OD=0.9mm, placed at the lumbar enlargement. In group B, rats had also femoral arterial line, polyethylene catheter, placed. Rats developing to extremities' paralysis were excluded from the study. On the 7th day after surgery, in each rat in group A, the effect of ITM, 0, 0.5, 10, 2.0, 5.0, 10, 20, 50 ug in 20 ul saline, on pain, at 15 minutes after injection was measured by tail flick test using 60'C hot plate, and on respiratory rate, at 30 minutes after injection, by thoracic impedance measurement technique. In each rat in group B, arterial blood was drawn to determine $PaCO_2$ at 30 minutes after ITM injection, the same doses as above. Two hours were left between measurements with each ITM dose. Statistical analysis was done on analgesic time, time until rats flick tails, respiratory rate, and $PaCO_2$ using paired t-test compared with those of ITM 0. P<0.05 was considered significant.

RESULTS: The results appear in Figure below.

Figure. The dose-response relation of ITM in rats.



DISCUSSIONS: ITM doses of 1 and 2ug are identified to be with significant pain relief and without respiratory depression.

REFERENCES: 1. Anesth Analg 1989;68:537-40.
2. Anesth Analg 1990;70:168-71.

S363

Title: THE EFFECT OF ALLOPURINOL ON REDUCTION OF OXYGEN RADICALS AND REPERFUSION ARRHYTHMIAS

Authors: MW Yang, MD, HL Hung, MD, WL Fen, MD, KH Chan, MD, TY Lee, MD

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Introduction: It has been proposed that the production of free oxygen radicals, for example by xanthine oxidase, play an important role in the genesis of ischemia and of reperfusion-induced arrhythmias. However, there is a lack of solid evidence to support this view. In this study, we evaluated the effect of allopurinol, a specific inhibitor of xanthine oxidase, on the reduction of oxygen radicals and of reperfusion arrhythmias.

Methods: With the institutional approval, we use an isolated perfused ischemic rat (Sprague-Dawley) heart preparation to conduct our study. A control group (n=30) received no drug and an experimental group (n=30) received allopurinol (100 mg/kgbw, intraperitoneal injection) prior to investigation. Ischemia was induced by the ligation of LAD. The incidence of reperfusion arrhythmias (by VF score) was observed. The concentration of H_2O_2 in pre-ischemic plasma and reperfused perfusate was determined by mass spectrophotometry (1).

Results: Our results showed no significant difference in the plasma H_2O_2 level between two groups at the pre-ischemic stage. H_2O_2 concentration of reperfused perfusate in the experimental group was significantly lower than those in the control group (see Table). The VF score in the experimental group also was lower than that in the control group (1.9±1.4 vs 3.07±1.8, P<0.01).

Table Comparison of H_2O_2 concentrations between two groups

	H_2O_2 Plas [μmol]	H_2O_2 Perfus [μmol]	Duration of VF (sec) (Frequence)
Control Grp.	24.7±8.1	3.5±1.9	216±82 (24/30)
Experi. Grp.	20±10	2.1±0.9**	117±32* (16/30)

* P<0.05, ** P<0.01: Compared between two groups

Discussion: From these results, we propose that free oxygen radicals formation by xothine oxidase, or its consequences, plays an important role in the genesis of arrhythmias. Effective pharmacologic control of arrhythmias may be accomplished by the use of elective oxygen radical scavengers (2).

References:
1. Anal Chim Acta 155:239,1983.
2. J Mol Cell Cardiol 17:485-493,1985.

S364

TITLE: ARE VAPORIZERS IN MOTION SAFE?

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Introduction: Anesthesia departments may consider utilizing gurney mounted vaporizers for transport of patients from one anesthetizing location to another. It is particularly an issue in transporting anesthetized children from an induction room to the operating theatre. However the ability of a modern vaporizer to deliver the desired concentration of vaporized agent in the inspired gas during motion has not been studied. Tipping of vaporizers has been reported to cause excessive delivery of agent to the patient sometimes resulting in cardiac arrest[1,2]. Because patients are potetially at risk, we measured delivery of gas from a vaporizer placed in motion and assessed the fluctuations in delivered concentration.

Materials and Methods: Fluotec II and III halothane vaporizers were filled to maximum level and securely mounted in the upright position onto a gurney. An oxygen E cylinder with a reducing regulator and flow meter delivered gas to the vaporizer. A Mapleson D circuit with 72 in. fresh gas line was attached to the output orifice of the vaporizer. Vaporizer output was sampled by a side stream port 6 in. distal to the gas outlet and analyzed using an Ohmeda RASCAL$_{TM}$. Data were recorded in real time. Oxygen was delivered to the vaporizer at 5 L/min flow. The system was calibrated at various dial settings using the RASCAL$_{TM}$. To verify that the system could respond to a sudden surge of anesthetic, a 0.1 ml aliquot of halothane was injected into the fresh gas line proximal to the sampling port, with the vaporizer in the off position. The resulting concentration of agent was measured.

The vaporizer was then set to deliver 1.0, 2.0, 3.0 and 4.0 % halothane on consecutive trials. After equilibration the gurney was accelerated from rest to walking speed and then to rest again. Additionally, the stretcher was agitated, turned around corners, pivoted abruptly on its axis, and driven over 3 inch speed control bumps. Lastly the stretcher was pushed head on into a fixed column while at a brisk walk to simulate a worst case scenario short of tipping the gurney over on its side.

Results: Injection of the halothane aliquot immediately (< 2 sec) registered in excess of 5.0 % for < 30 secs. on the RASCAL$_{TM}$. None of the movements described above resulted in a fluctuation > ± 0.1% of the delivered concentration of halothane from the set concentration of (1.0-4.0%) as measured by the RASCAL I$_{TM}$.

Discussion: We conclude that this experimental design is capable of detecting sudden surges of halothane that may come from the vaporizer. Additionally, a securely mounted upright Fluotec II or III vaporizer delivers the desired concentration of anesthetic despite motion and is not analogous to tipping the vaporizer. Additional tests need to be performed with other vaporizers and in other conditions to further delieate the safety of vaporizers in motion.

References: 1. Anesthesiology 26:235, 1965. 2. Med J Aust 1:1108, 1969.

S365

Title: SPINAL ANESTHESIA REDUCES BEAT-TO-BEAT HEART RATE VARIABILITY

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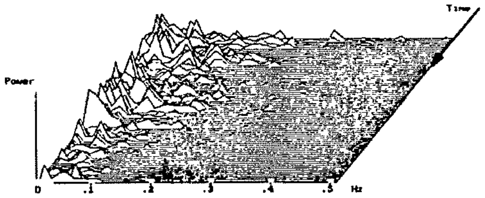
Introduction: Sympathetic (S) and parasympathetic (PS) modulation of cardiac rhythm produces heart rate variations (HRV) that occur at frequencies below 0.5 Hz[1-2]. Oscillations of 0.1 Hz or less are attributed primarily to S stimulation, while oscillations of 0.15 Hz or greater are believed to be indicative of PS activity. This study was undertaken to determine if autonomic regulation of cardiac rhythm is compromised during spinal anesthesia.

Methods: With institutional approval, ECGs were recorded from patients receiving a spinal block anesthetic. The ECGs were recorded using a SpaceLabs 90603A patient monitor and stored on magnetic tape. Data were analyzed by computing sequential power spectra from the taped ECG records. The power spectral records were obtained by passing the raw ECG signal through a Hewlett Packard 8812A heart rate computer which produced a continuous beat-to-beat record of heart rate. This signal was then subjected to Fourier analysis using a Tektronix 2630 spectrum analyzer interfaced to an IBM AT type computer running analysis software from Tektronix called SPECMAP.

Results: The amplitude of HRV power spectral peaks decreased when spinal blockade reach the T_5-T_6 dermatome level. Decreases in peak amplitudes were limited almost exclusively to frequencies above 0.1 Hz until sensory loss reached the T_4 level. For blocks at or above the T_4 level, power spectral peaks decreased for all frequencies. Those above 0.1 Hz were virtually eliminated. No changes were observed in the power spectra of patients with failed blocks. An example of an HRV power spectral response is shown in figure 1. Each trace resulted from the analysis of 80 s epochs of heart rate data.

Discussion: Although one might expect loss of sympathetic activity during a "high" spinal, the data suggests that autonomic activity is altered by "normal" levels of spinal block. The reduction of activity within the frequency band associated with PS stimulation probably reflects a reflex response to a partial loss of S activity.

Figure 1



References:
1.Akselrod S, et al. Science 213:220, 1981
2.Saul JP, et al. Am J Physiol 258:H713, 1990

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S366

Title: SUBJECTIVE, PHYSIOLOGICAL AND BEHAVIORAL RESPONSES TO INTRAVENOUS DEZOCINE IN HEALTHY VOLUNTEERS

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Introduction: Dezocine is a recently FDA-approved opioid agonist-antagonist that acts at the mu receptor, and is primarily used in medical settings for management of pain. Dezocine is self-administered by monkeys[1,2], and in former opiate addicts, dezocine has a spectrum of subjective effects similar to that of morphine[3]. We asked the question whether this narcotic had a spectrum of pleasant subjective effects in healthy volunteers - such results would suggest that people who do not have a history of opiate abuse, but with ready access to the drug (such as medical personnel), might like it, and come to abuse it.

Methods: After IRB approval, we examined in healthy volunteers (N=10) the subjective, physiological and behavioral effects of intravenous dezocine. A within-subjects design was used in which subjects (6 males, 4 females; mean age: 22±1.5 yrs; mean weight: 72±14.7 kg) were injected with 0, 2.5, 5.0 and 10 mg/70 kg of dezocine in a double-blind fashion. Subjects completed several questionnaires commonly used in abuse liability testing studies, and several psychomotor tests, before drug injection and at periodic intervals for up to 5 h after drug injection.

Results: Psychomotor functioning (e.g., Digit Symbol Substitution Test) was impaired by dezocine, but only at the highest dose tested. Miosis (constriction of the pupils) occurred in a dose-dependent fashion. Dezocine produced a spectrum of subjective effects which included liking (as assessed by a VAS) for the drug ($p<0.005$). Interestingly enough, self-reported liking of 2.5 mg/70 kg dezocine was similar to that of the two higher doses. Scores from a 'euphoria' scale from a standardized drug effects questionnaire, the Addiction Research Center Inventory (ARCI)[4], increased after dezocine ($p=0.10$), but like drug liking, was not increased in a dose-related fashion. Other subjective effects which might be considered as pleasant ('good mood,' 'drunken,' 'coasting,' 'high' ratings) were increased by dezocine (all $p<0.05$). Although scores from the 'dysphoria' scale of the ARCI increased after dezocine injections, other effects indicative of dysphoria (e.g., 'nauseous' and 'sick' ratings) did not change as a function of dezocine dose.

Discussion: The subjective effects of dezocine across a 4-fold range of doses in healthy volunteers, in general, produced a spectrum of pleasant subjective effects which would not have been predicted from earlier studies of opiates in healthy volunteers[5,6]. Our results call into question the fact that dezocine is not currently scheduled by the Drug Enforcement Agency and has less stringent controls on its accessibility than Schedule II narcotics like fentanyl or morphine. Based on the results of our study, and previous studies with this compound[1-3], we believe dezocine should be regulated to a greater extent, to reduce the probability of people with ready access to the drug experimenting with it, and perhaps subsequently abusing it.

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1 Pharmacol Biochem Behav 14:241-245, 1981
2 J Pharmacol Exp Ther 229:118-126, 1984
3 Drug Alc Depend 38:544-548, 1985
4 Clin Pharmacol Ther 12:245-258, 1971
5 JAMA. 157:1006-1020, 1955
6 J Pharmacol Exp Ther 136:47-52, 1962

S367

Title: PHENYLEPHRINE FOR HYPOTENSION IN HIGH RISK PARTURIENTS DURING CESAREAN SECTION

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Introduction: Phenylephrine (Phen) has been used for treating maternal hypotension in healthy parturients (1). This study evaluates Phen in high risk parturients.

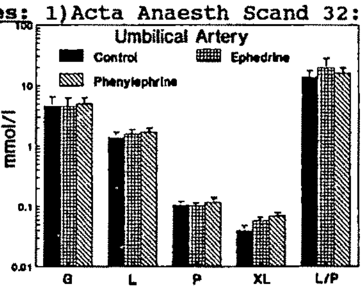
Methods: Informed consent and review board approval were obtained. High risk parturients (n=45, diabetes mellitus, severe asthma, drug abuse, twins, preeclampsia) undergoing cesarean section under epidural anesthesia were studied. Patients received 1500 ml of Ringer's lactate. Those who developed systolic hypotension (<90 mmHg or a 30% decrease) were randomized to receive ephedrine 10 mg (Eph, n=18) or Phen 100 µg (n=16). Patients not requiring vasopressor (n=11) served as controls. At delivery, maternal arterial, neonatal umbilical venous (UV) and arterial (UA) blood PO_2, PCO_2, pH, lactate (L), pyruvate (P), glucose (G) were measured. The results (mean ± 1SE) were analyzed using ANOVA at $p < 0.05$.

Results: No significant differences occurred in disease states, Apgar scores or birth weight. No significant differences occurred in baseline, hypotensive and post-therapy blood pressures and heart rate between the Eph and Phen groups. Neither maternal or neonatal acid base status nor other indices of anaerobic metabolism including excess lactate (XL) differed among the groups (Table, Figure).

Discussion: The use of Phen for treating maternal hypotension during cesaren section produces neonatal and maternal outcome similar to that seen with ephedrine. No evidence of fetal lactic acidosis was seen with Phen.

References: 1)Acta Anaesth Scand 32:559,1988

Figure



Table

		CONTROL	EPHEDRINE	PHENYLEPH
UA	pH	7.26±.02	7.25±.01	7.22±.02
	pCO_2	47±5.3	53±2.3	54±4.5
	pO_2	22±5	16±1.5	15±1.3
	BE	-5.7±2	-3.2±1	-4.3±1.8
UV	pH	7.30±.02	7.28±.01	7.3±.02
	pCO_2	40±3.5	44±1.6	43±2.7
	pO_2	30±3	29±1.7	25±1.4
	BE	-5.7±1.5	-4.9±1	-4.2±1

S368

Title: DEXMEDETOMIDINE EVOKES FREE INTRACELLULAR CALCIUM SURGE IN ASTROCYTES BUT NOT IN NEURONS

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Introduction: Free intracellular calcium (Ca^{2+}) serves as an essential intracellular messenger in virtually every type of cell. A steep Ca^{2+} gradient exists across the cell membrane and this gradient is maintained by Ca^{2+} channels, active carrier-mediated transport and binding to or release from calcisomes. It is known that stimulation of alpha-1 adrenergic receptors leads to increased phosphotidylinositol metabolism and influx or release of Ca^{2+} (Bylund, 1983). Less is understood regarding the distribution and function of alpha-2 adrenergic receptors.

Neuronal-astrocytic interaction is important in the function of the central nervous system (CNS) (Hertz, 1989). It is well-established that astrocytes exhibit several adrenergic receptor subtypes that regulate different intracellular processes and that norepinephrine increases free intracellular calcium in astrocytes. In this work we have studied whether the highly specific and potent alpha-2 agonist dexmedetomidine (dex) affects intracellular calcium in cultured neurons or astrocytes.

Method: Primary cultures of astrocytes or neurons were prepared from newborn mouse neopallium or developing cerebellum and grown on cover slips in nutrient medium. Cover slips of cells were treated with the fluorescent dye Indo-1 and emitted fluorescence measured at two wavelengths (400/500 nm). Free intracellular Ca^{2+} levels were determined during superfusion with a control saline, with or without drugs added, followed by a calcium calibration. (Grynbiewicz, 1985).

Results: Dex caused a four fold increase in free intracellular calcium in astrocytes with peak effect at 100 nanomolar. There was no response in neurons even at 2 micromolar. Norepinephrine showed a similar response to dex but required higher concentrations.

Discussion: To date the only example of alpha-2 agonists causing increased Ca^{2+} concentrations is in smooth muscle (Salm & McCarthy, 1990). Our observations demonstrate that the potent alpha-2 agonist dex, an anesthetic adjuvant, affects calcium concentration in astrocytes, but not in neurons from the CNS. The correlation between this effect and its pharmacological action is unknown.

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